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RADIATION BURNS, INCLUDING VOCATIONAL AND ATOMIC EXPOSURES. TREATMENT, AND SURGICAL PREVENTION OF CHRONIC LESIONS*

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A STUDY OF the development, pathology, course, and treatment of radiation lesions was recorded[1] in May, 1949. Further work, including repair of atomic radiation lesions and the surgical prevention of chronic radiation burns, is reported here, with a summary of essential findings from the first publication.

The value of radiation therapy and x-ray examination is not underestimated, and no suggestion is intended as a directional approach to problems in the use of radiation in any form. It is hoped, on the other hand, that discussion of possible unfortunate ultimate results of radiation may lead to prevention, recognition and elimination of these burdensome troubles. It is further hoped that the suggestion of "changing" the skin in an involved area *before* serious trouble develops may lead to even wider application of radiation therapy and even more brilliant results (Fig. 8).

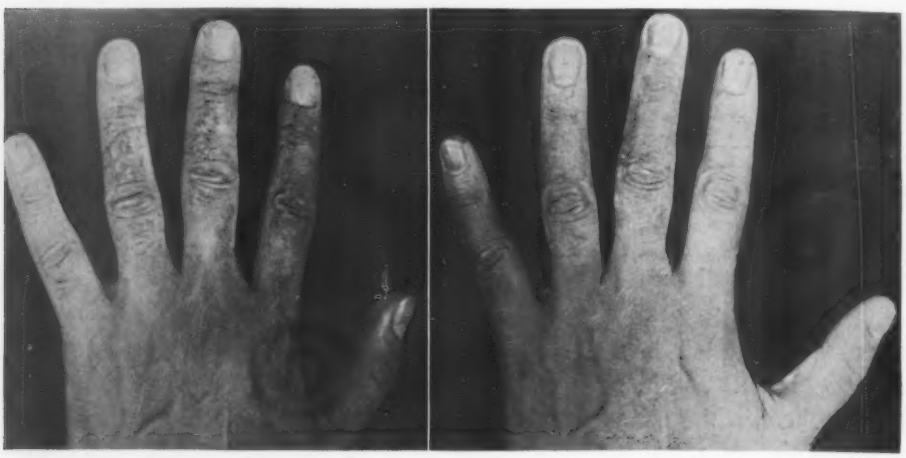
Diagnosis of radiation lesions should be easy from appearance and histories. It is mentioned here only to suggest that the element of suspicion that such a lesion might exist has been lacking in some instances, and progress of the trouble has continued, often with irritant forms of therapy being added. This occurs in doctors themselves as often as in any group.

Sources of burns are vocational, as in doctors (Figs. 1 and 2) and dentists; therapeutic radiation, either in known huge dosage or accumulative small doses (Figs. 3, 4, 5) as for acne; diagnostic, as in fluoroscopic examination, the lesions of which are frequently missed in diagnosis because of lack of history or lack of suspicion; commercial epilation (Fig. 6), this being a source of damage that seems the most useless; and atomic radiation, either in laboratory or test workers, or, of course, victims in war time (Fig. 7).

* Read before the American Surgical Association, St. Louis, Mo., April 20, 1949.

ACUTE BURNS

These result from large single exposures, or from exposures repeated closely over a short space of time, or from atomic radiation, and should have a conservative plan for their treatment, especially as far as amputation of extremities goes. Rest, sedation, prevention of infection, and alleviation of the severe pain are carried out, as well as grafting of open wounds as soon as it is felt that a free graft or flap will survive. For burns of known surface extent, early excision and repair may be done, but even in these instances there may be surrounding involvement by a chronic process that becomes apparent later.



A B

FIG. 1.—(A) Fluoroscopic burns in surgeons fingers; fairly rapid development in three years' time. (B) Result of resection and repair with free split skin grafts. One operation. Function and freedom of trouble obtained and patient able to scrub for surgical work.

CHRONIC BURNS

The chronic burn is the type usually thought of, such as those seen in the hands of doctors. These result usually from repeated small exposures over a long period of years, and the lesions are always getting worse. Acute burns from single exposures may result in the development of chronic changes also, and for this reason, after subsidence of the acute stage, trouble still may be expected.

The lesion in the skin is dangerous because it is a progressive one with the ultimate stage of carcinoma being in sight—if the patient lives long enough. Doctor Wolbach studied *the pathologic changes* and reported them essentially as coagulation, atrophy, endarteritis of the small arterioles, a compensation telangiectasis, clotting of the dilated vessels which gives the "coal spots," epithelial activity to throw the "coal spots" off, which in time causes keratosis, ulceration, and finally, after a long continued wound stimulus, carcinoma. This course requires five to 25 years, but is always progressive.

The usual type of carcinoma is squamous cell, but basal cell growths and even sarcomas may occur. This slow irreversible process of continual epithelial activity, trying to cast out the intradermal foreign bodies of clots and necroses, is perhaps the closest approach we have clinically to an ultimate cause and development of carcinoma.

It is possible that the effect on the vessels on the venous side of the circulation is important also in the changes that become irreversible. This involve-

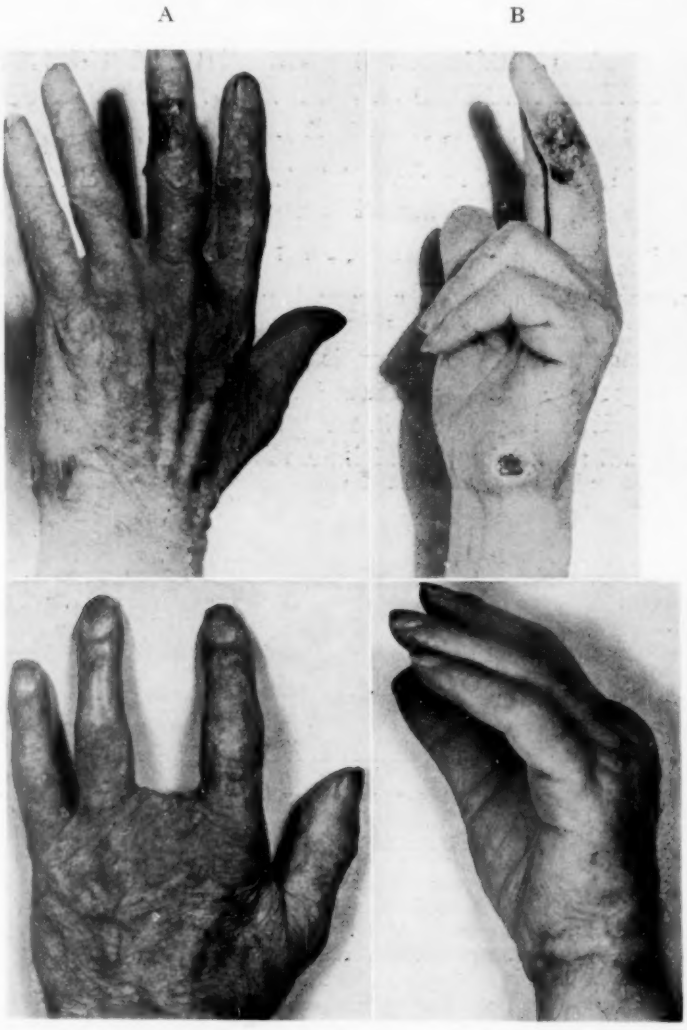


FIG. 2.—(A and B) Hands of surgeon (A. S. A.) with vocational burn from disregarding his own safety in interest of patients, with carcinoma having developed in several areas. (C) Early result of wide deep resection and grafting, and of removal of finger that could not be repaired.

ment is of no special clinical significance, but is mentioned as an addition to the pathologic process recorded.[1]

Effective treatment for the usual chronic burn is excision, and repair of the defects with free skin grafts or flaps. A paradox is that treatment should be done early, or in a quiescent stage, rather than in an ulcerated infected stage. This is hard to get even doctors to go through with; but if there is pain as well, this is an impetus to operation. Removal of the area results in immediate relief of pain, and the patient usually makes this escape the subject of his first

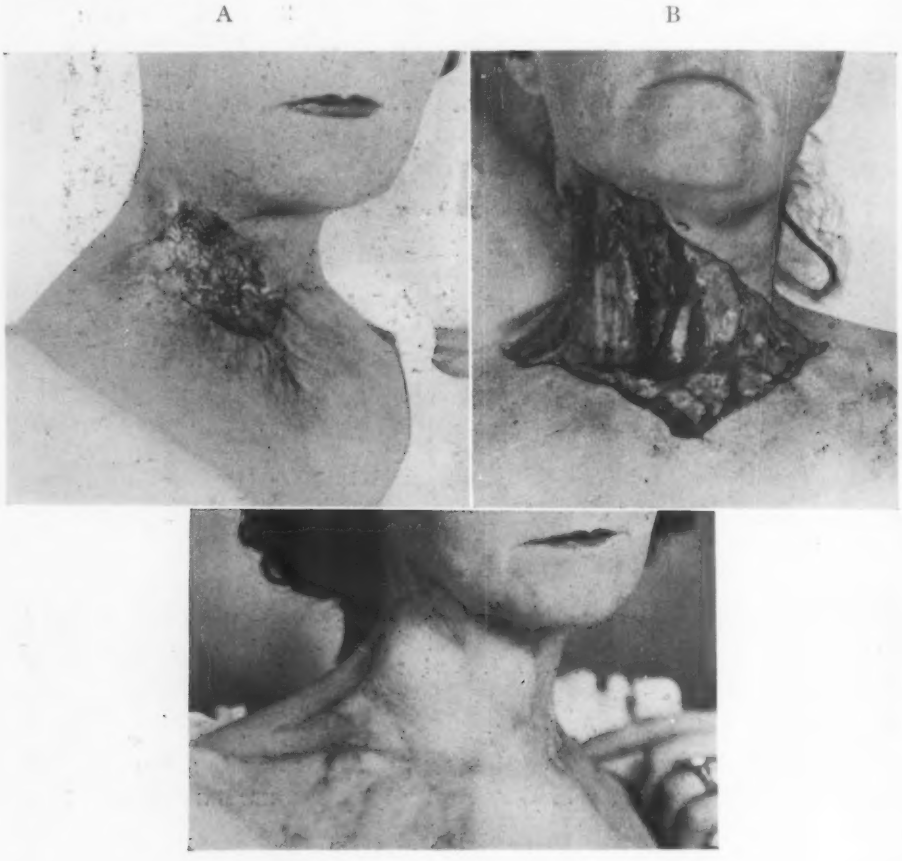
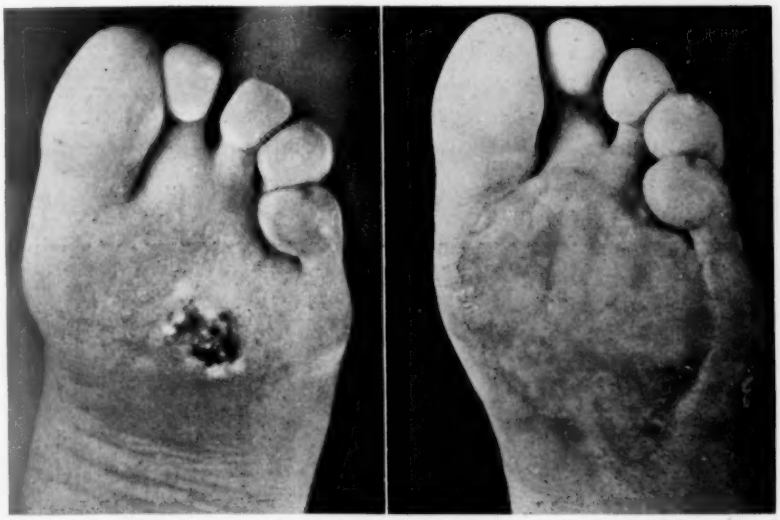


FIG. 3.—(A) Carcinoma in radiation burn from treatment of thyroid. (B) Wide deep resection, including sternomastoid muscle and internal jugular vein, extending to trachea. (C) Repair with pedicle flap from chest.

expression on recovering from the operation. The repair of the excised lesion may be done either primarily or secondarily, and there are many points of importance in designing and carrying out repairs of these resultant open areas, especially when features are involved.

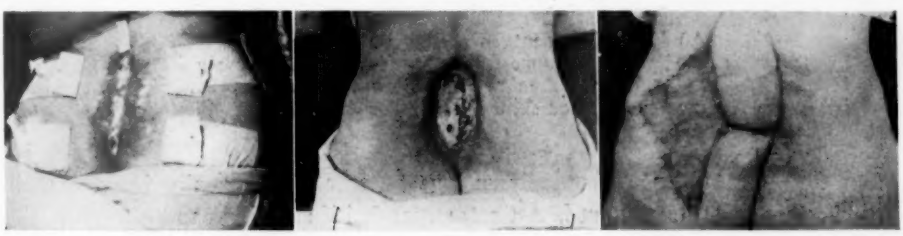
In hands, especially those of doctors where the fingers have to be dealt with, a conservative approach should be made in view of possible trouble with circu-

lation. Both the palmar and dorsal surfaces should not be done at one time, and if the palmar surface does have to be done, great care should be taken with the blood and nerve supply in the dissection and in the dressing to prevent trouble. It is imperative that at least one artery be maintained, and even then



A B

FIG. 4.—(A) Extensive change following roentgen ray treatment for plantar wart, with carcinoma having been removed previously from the burn. (B) Result of wide deep excision and repair with thick split graft; one operation. When there is sufficient soft tissue pad on the sole, free grafts can be used. Otherwise, pedicle flaps are required.



A B C

FIG. 5.—(A) Radiation burn following treatment for fibroids. Spinous processes and ligamentum nuchae involved with excessive discomfort and pain. (B) Resection without immediate repair because of exposed bone and ligaments. Pain relieved. (C) Repair with adjacent flap and grafting of donor site of flap.

trouble with circulation may develop if there is sclerosis of the vessels beneath the excision.

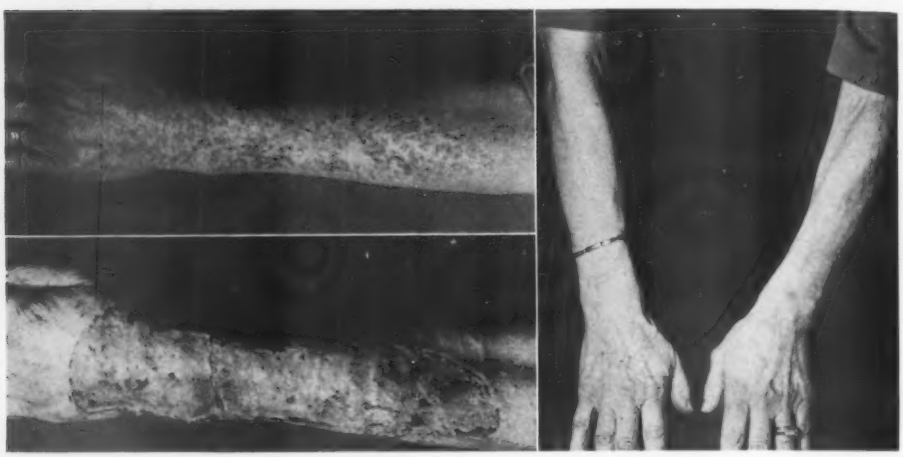
When there is known circulatory trouble present, it may be best to do cautery removal of isolated keratoses or ulcerations and allow them to heal individually. A balance is that all possible fingers should be saved, but fingers

that have dangerous growths or hopeless function should be considered for removal.

On the palmar surfaces the skin is so keratosic anyway that the typical gross appearance may be misleading and the diagnosis confused for excessive keratosis of other origin.

The lesion, once developed, is irreversible as far as is now known, and further radiation of any form as treatment might have the term malignant applied to it. Occasionally, in late chronic burns with carcinoma already developed, some protective or temporary radiation might be directed toward the malignancy. If there is the possibility of alleviation of the carcinoma, this area

A



B C

FIG. 6.—(A) Extensive roentgen ray burn following commercial epilation treatment. (B) Immediate appearance following resection and repair with split grafts. One operation. (C) Result 17 years later, showing normal appearance and persistence of function of the grafted skin.

and the surrounding chronic burn can be treated surgically later, but this further radiation treatment is not recommended if excision can be accomplished primarily.

Management of regional nodes where carcinoma has developed may be the same as for other carcinoma. These carcinomas do metastasize, and small original lesions have proved fatal.

Persistence of function in repairs after excision of chronic radiation burns usually occurs and the new skin covering lasts throughout life. The patient in Figure 6 is shown after 17 years, and may be expected to go on without further trouble, and others are known to be free of trouble over longer periods. It may be occasionally indicated to do secondary excision and repairs because of surrounding tissue change several years after what has been thought to be a satisfactory removal. This problem may have to be dealt with about the face,

where some limitation of excision may have been done originally to avoid damaging a feature.

It may be found that there is too much deep fibrosis and necrosis to permit of immediate repair. In the popliteal region, to avoid nerves or vessels, and on the sole of the foot, especially in acute fluoroscopic burns, the excision may not be carried deep enough to arrive at an adequate minute blood supply that will carry either a free graft or a flap. These areas may be "dressed" with split grafts to get all possible take and finally be repaired later, or the areas may be left open. These points come under the statement above, that complicated problems of plastic reconstruction may arise.

Late necrosis of underlying structures such as bone and tendon may occur occasionally in severe burns and require excision, or amputation of fingers, as reported by Dr. S. L. Koch in the discussion of this paper.

Growth interference or failure of development to normal size of areas following radiation in infancy and childhood may occur, especially about the face. These areas may require replacement of overlying skin and restoration of features and this might come under the title of radiation burns, but problems here are essentially plastic surgery problems.

Chronic atrophy, whether diagnosed as a burn or not, will probably show up in practically every tumor area treated with radiation. If it were recognized that this might happen and that the atrophic skin should and could be changed, then some resistance to radiation therapy might be overcome.

Atomic radiation lesions may increase as work in turning mass into energy increases, and the incidence in the next war may be tremendous.

In time of war, fire and blast injuries may be greater in number than radiation injuries, but some of those surviving the blast and fire, and possibly many relief workers, will suffer radiation burns, and these lesions are under consideration here.

Enough burns have been encountered among workers in the development and production stage of atomic work to give indications of what to expect. The lesion produced by atomic radiation is not a new one entirely, but the time element of the development is faster than in the accumulative x-ray burn, due to the excessive exposure in a short space of time. These burns usually arise from mistakes in security precautions, and add the ever present human element to the ultra in scientific work.

Whether the radiation is Beta or Gamma may not be definite in some exposures, but as far as can be determined now the burns probably occur from both Beta and Gamma radiation. Because of excessive dosage, symptoms may begin very soon after exposure, and blistering may occur in four to six days. The blistering runs its course in about 30 days and there is either healing or sloughing, with resultant open wounds according to the degree of the exposure. Exposures heavy enough to be fatal are not for discussion here.

Conservative treatment, especially about the hands, avoiding early amputation, is indicated because hopeless looking fingers finally may be spared (Fig. 7). Relief of pain, prevention of infection, and general supportive measures

are the main items of treatment. Blood changes are not significant in patients with exposures over small areas, but there may be emotional disturbances in workers that require patient guidance, with recreating of hope for ultimate survival of the damaged parts.

Since these accidents are apt to be of excessive local exposure, (12,000 r in a few seconds), more sloughing and ultimate atrophy may be encountered

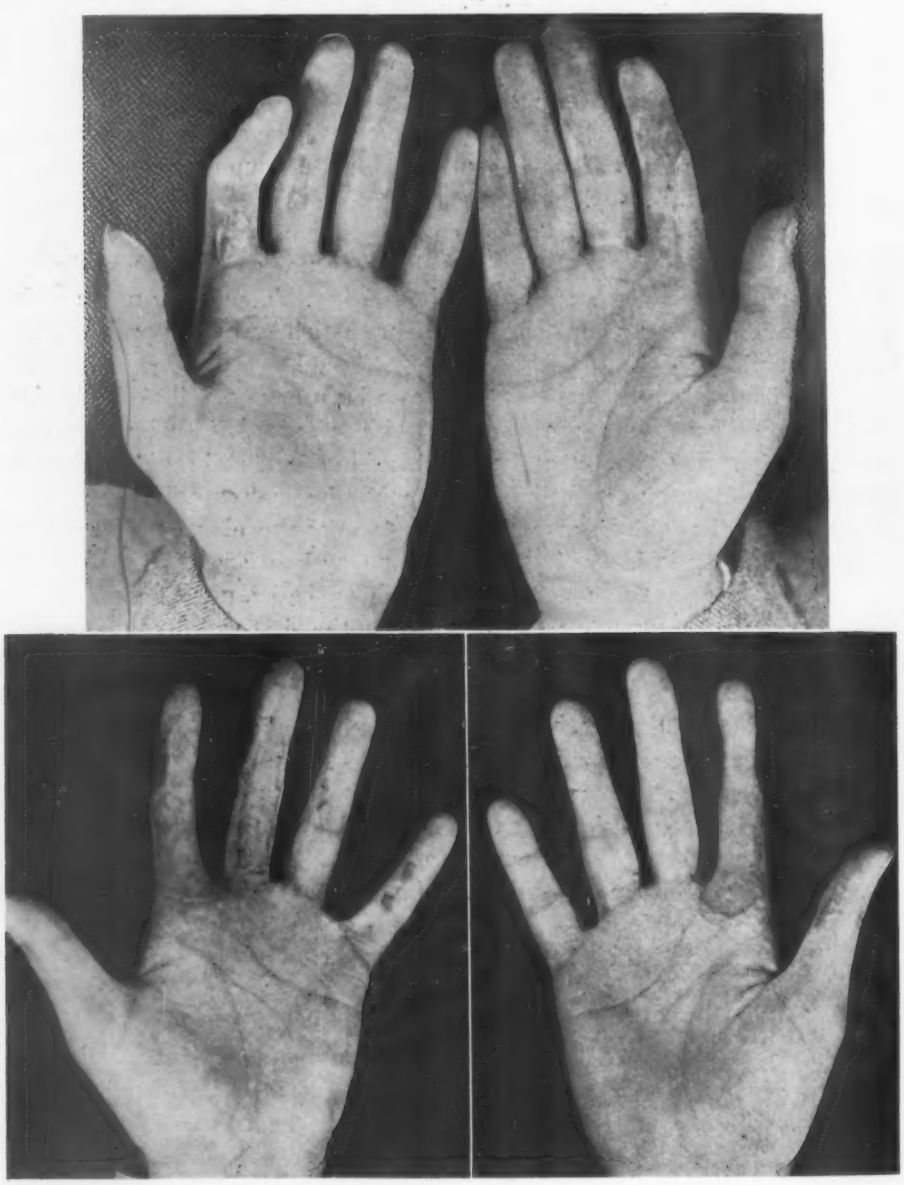


FIG. 7.—Examples of atomic radiation burns which have been treated conservatively in acute stages and are being repaired by resection and thick split skin graft repair.

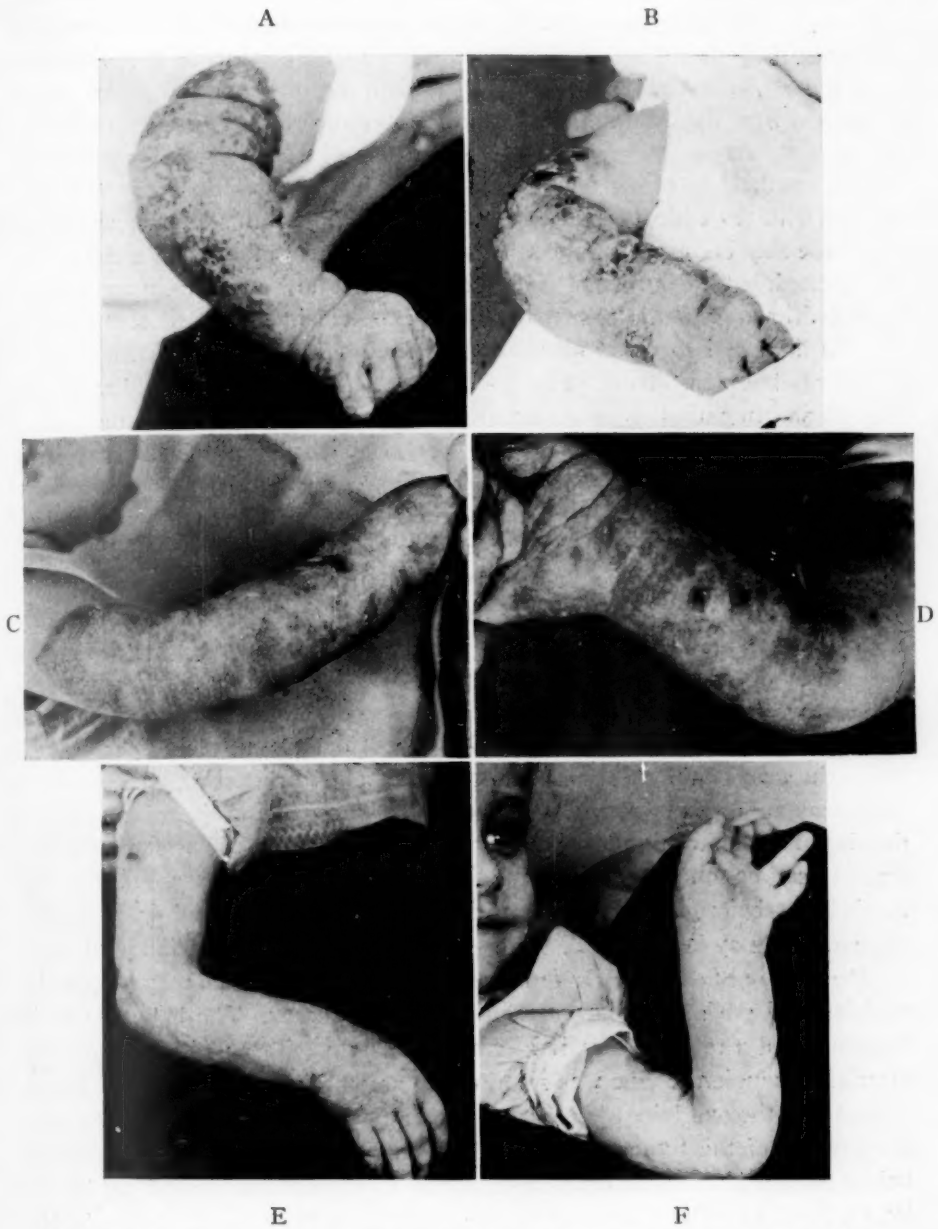


FIG. 8.—Prevention of chronic radiation lesion by resection and repair of area before chronic changes occur. (A and B) Active arterial neoplastic hemangioma involving skin of entire arm. Amputation had been recommended. (C and D) Arm with control of the active hemangioma by x-ray treatment given by Dr. W. G. Scott and Dr. Sherwood Moore. (E and F) Arm entirely covered with thick split grafts after resection of the skin which wasn't normal anyway, and which would have gone into chronic changes requiring removal. Two operations.

than in the usual x-ray burn, so that more amputations may be required. The pathologic processes may seem more contracted in time; that is, the various elements of tissue changes may develop faster than in the usual chronic radiation burn. This also is probably dependent on the large, sudden, single exposure. But these differences do not change the rule of being conservative in the acute stage.

The pathology seems to be close to that already described for radiation burns (with the added sloughing and atrophy) and for this reason, at least as far as the skin is concerned, the same idea of treatment of excision and grafting is indicated, but the burns are too recent to predict how soon carcinoma may be expected in ungrafted areas. It could be expected in ungrafted areas earlier than in the usual chronic radiation burns from accumulative exposures.

In summary for atomic radiation burns it may be said that they are probably similar in pathology to the usual radiation burn. The lesion in the skin is probably a progressive one after it is once established, and instead of getting better it will tend to get worse. Conservative treatment, especially in reference to amputation, should be carried out in the acute stages. When there is subsidence of the acute stage, open areas may be grafted to hasten healing. When the chronic stage develops and the lesion in the skin is troublesome and its progressiveness is recognized, the involved areas may be excised and grafted with free grafts or covered with flaps as indicated. Pain will almost always be relieved by operation, and the new skin in the area will probably survive without further change, unless there has been deeper damage that will undergo necrosis from failure of blood supply because of damage to the deeper vessels. After the area of the most acute burn is controlled by excision and grafting, there may appear later a chronic change in the surrounding tissues, and if this develops into a chronic radiation burn, the same process of excision and skin grafting can be followed as for any other chronic radiation burn. This is best carried out before too much ulceration has developed. Possibly some late amputations may be indicated, but the conservative rule can be followed.

Prevention of chronic skin lesions in heavily radiated areas may be done by excision and grafting *before* the chronic changes occur. The baby shown in Figure 8 had a total involvement of the right arm with an active, neoplastic, arterial hemangioma. She was sent in with amputation recommended. It was known that the overlying skin was no good anyway, and it was thought that if the activity of the tumor could be stopped, then the skin could be changed before serious late lesions developed. X-ray treatment was carried out by Dr. W. G. Scott and Dr. Sherwood Moore, and the brilliant result shown in (b) and (c) was obtained without further activity of the tumor occurring.

The scarred skin of the entire arm was then resected, and replaced with thick split grafts in two operations, and the child has normal function and no further trouble. To all appearances, complete rehabilitation has been effected. This saving of the arm by radiation, and the prevention of the late bad effects of the therapy by surgical resection and restoration with skin grafts, is thought

to be of worth-while consideration, and possibly to open up wider fields of usefulness in the radiological management of serious crippling lesions.

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Due to unforeseen difficulties, some illustrations of facial lesions were omitted at the time of publication of this article.

DISCUSSION.—DR. ROBERT H. IVY, Philadelphia: A considerable proportion of the practice of the average specialist in plastic surgery is the repair of damage caused by irradiation—frequently, it is true, following justifiable treatment for cancer, but just as often for benign conditions where primary surgical treatment would have avoided this damage and rendered late secondary operations unnecessary in many cases.

I can only confirm what Dr. Brown and his associates have stated regarding the indiscriminate use of x-rays and radium for benign growths and inflammatory and other skin lesions. This irradiation damage does not occur only in the hands of the inexperienced radiologist. We have seen many cases from the clinics of men of the highest standing and experience.

I believe much good could come from presentation of a paper of this type at one of the large radiological meetings, because many radiologists do not seem to be aware of these late reactions.

The slides represent one or two cases of irradiation damage requiring excision of the lesions and secondary repair of the resulting defects.

May I close by quoting the last sentence from an editorial in the Journal of the American Medical Association for September 18, 1948 (**138**: 214, 1948), entitled "The Hazards of X-Ray": "Roentgen treatment for benign conditions should be used only with a vivid appreciation of its capacity for harm, and with an overt evaluation of its presumptive benefits weighed against the known and possible injuries inseparable from its use in effective dosage."

DR. SUMNER L. KOCH, Chicago: I am sure every one of us would be happy to secure results such as Dr. Brown and Dr. Ivy have shown here. In listening to Dr. Brown's discussion of this problem and seeing his cases, I am always impressed with the difficulties and the serious problems which they present. I am also impressed by the fact that none of these difficult cases are turned away, but that they are helped and often almost unbelievably improved.

I would like to show two cases, the first an acute radiation injury much like that of the young doctor whom Dr. Brown showed.

(Slide) This patient came to us after having spent two days before Thanksgiving and the day after, examining fuses under a fluoroscopic screen. She had spent a total of 24 hours at this work and came to see us ten days later.

(Slide) At that time her fingers looked as though they had been extensively infiltrated with a local anesthetic. They were red, white, over areas of greatest tension, and greatly swollen.

(Slide) After about a week of daily dressings the sloughing skin separated.

(Slide) We were able then to apply skin grafts over the raw surfaces.

(Slide) The skin grafts healed kindly, and for two years the patient was able to continue her regular work. Then she returned with degenerative changes beginning to appear beside the areas which had been grafted.

(Slide) Since that time it has been necessary to remove the greater part of the distal phalanges of the four fingers of the right hand. On the lateral side of the thumb the bone is becoming exposed over the proximal phalanx, and we are still faced with the problem of further surgical work on this patient.

This case emphasizes the fact that the care of these cases is a continuing problem.

(Slide) A second type of case which has proved difficult for us has been the patient with injury of the ventral and dorsal surfaces of the lower trunk after excessive radiation for an abdominal tumor.

(Slide) This patient was treated by raising flaps from both buttocks and rotating them medialward. A part of the flap which was to cover the sacrum was lost, and it was necessary to complete the repair with free grafts. Healing has now persisted for two years. The fact that the radiation injury always extends more widely than is apparent from a surface examination adds to the hazard in raising and transferring a flap in these cases.

(Slide) A year after the first series of operations the irradiated area on the ventral surface broke down, and it was necessary to carry out repair of this area.

(Slide) This was accomplished by wide excision and covering of the raw surface with a single pedicled flap.

DR. RUDOLPH MATAS, New Orleans: I cannot resist the temptation to join in this discussion, as x-ray and radium burns have a special appeal to the men of my time, in whom pioneering in x-ray and radium therapy was somewhat of an adventure involving risk to both the doctor and patient. Ignorance of the proper technic, lack of experience, and the universal curiosity to see the rays at work searching for lost bullets or foreign bodies, or the setting of broken bones, led to prolonged exposure of the patients in various parts, and of the doctors' hands, without adequate protection. It was only until many disasters, including amputations, hastened the development of a better technic that finally, as at present, the dangers of x-ray and radium burns have become practically negligible in competent hands. But the reports we have just heard show that notwithstanding all the improvements in radiology, the risk of late necrogenic dermatitis and malignant transformation of the irradiated areas still exists and is far from negligible.

I recall many young medical x-ray pioneers who suffered from x-ray burns of the hands caused by prolonged exposures without adequate protection; and it is in this group that the chronic radiodermatitis, followed by cancer of the fingers and hands, were most frequently incurred.

I am well acquainted with the young Spanish surgeon referred to by Dr. Brown. He was following a course in plastic surgery and availed himself of the opportunity to get rid of a chronic radiodermatitis which he feared was the precursor of cancer. I am pleased to confirm that Dr. Brown's excision of the affected areas, followed by grafting, has yielded excellent results, physiologically and cosmetically, leaving the fingers and hand free to perform the most delicate plastic operations. The fingers of the opposite hand, showing a marked tendency towards subsidence of the eruption, were not operated upon.

Incidentally, x-ray and radium burns are exceedingly painful, and I do not believe anything exceeds the constant torture of a radium burn. The relief of pain is therefore a great problem in dealing with x-ray and radium burns. Extirpation of the burned areas is the most certain mode of obtaining relief, but the practice of excision was not generally adopted until about 1908 and 1909, when Charles Allen Porter of Boston began his advocacy of excision in precancerous lesions. But extirpation is not applicable to all cases, especially those involving certain widely spread and vital areas. Innumerable formulas were devised and tried, almost all the effective ones ending in mixtures containing opium. It is interesting to recall, however, that one lotion did, unexpectedly,

come to the rescue after a long gamut of soothing and healing dermatological applications had been tried and failed. This remedy was the so-called "Fisher Fluid," which I first saw announced in the London Lancet of October 29, 1913. It is named after Dr. J. L. Fisher, Director of the Municipal X-ray Clinic at Copenhagen, Denmark. It is purported to be a compound of horse serum treated with Trypsin, freed from coagulable substance, *horse saliva* and ½ of 1 per cent carbolic acid as a preservative. This fluid, which became known in the trade as "incitamin," had a very considerable circulation in America, once its soothing and healing properties became known. It was applied to the diseased surfaces on gauze compresses soaked in the fluid, the gauze kept always moist. The second world war interrupted the importation and the manufacture in this country. It was claimed that incitamin was a specific. It certainly relieved pain and aided as nothing else did.

One of the most terribly impressive and distressing examples of the cruel and deadly effects of the x-rays when applied in massive (brutal) and prolonged doses and delivered at a short distance upon an unprotected surface, was that of a young woman from Vicksburg who had been treated for a small non-toxic goiter by an ignorant and unscrupulous quack. This happened in the winter of 1898, close to the beginning of the Roentgen era.

When I was called to see this patient she was practically moribund, in a stupor from a profound toxemia and marasmus caused by an acute necrotic laryngo-pharyngitis, with almost total obstruction of the air passages compelling an emergency tracheotomy, and an acute inflammatory stricture of the pharynx and upper esophagus, blocking the way to all food and drink. Widely diffused radio-dermatitis had spread over the neck from the chin to the sternum. The skin was intensely cyanotic about an incision to evacuate pus, plus a necrotic laryngeal cartilage. Pneumonia, with edema of the lungs, fortunately brought on an early end to this fearful, gruesome pre-cadaveric picture.

Another phase of the x-ray problems which still remains as a sequel to therapeutic radiation—the predisposition, or transformation, or metaplasia of radiated tissue, to cancer, the "x-ray cancer"—is tragically and most impressively told in the story of Dr. E. K. of New Orleans, one of the dental profession's most distinguished leaders, and the first in the world to demonstrate the enormous diagnostic value of the x-ray in dental practice (1896). Dr. K. had begun experimenting with x-rays almost immediately after Roentgen's epochal discovery (1895). Dr. K., though one of the greatest masters of x-ray technic, shared the fate of his early radiologic contemporaries, who, in exposing their hands freely to the rays, developed a radio-dermatitis which predisposed to malignant infiltration, which in this case began at the finger tips of the left hand and spread from one finger to another and then to the hand, compelling the amputation of these parts. But this was only the beginning of a series of amputations which followed in quick succession from the hand to the forearm and up the arm to the level of the armpit. In all, 35 operations were performed. Finally, when malignant ulcerations began at the stump of the arm he began to cough and expectorate blood. This was the last line of defense. All the signs announced that the vital citadel had fallen in the hands of the enemy. He had endured the pain and the continued distress of three years of suffering. He had reached the limit of endurance, and, though a tremendously courageous and determined man he could go no further, and on the morning of May 7, 1928, he was found dead in his office with a bullet through his brain. That is how this heroic sufferer put an end to his martyrdom and found relief.

Strange as this paradox seems of the subservience of radiation to cancer, it is more easily explained than the, at one time, mysterious process by which the tissues—after having been successfully x-rayed for the prevention of recurrence after operations for malignant disease, or further prophylactic purposes—retain a necrotizing potentiality in the radiated areas which does not manifest itself until the lapse of months or years, even three and four years, after the prophylactic rays have been applied.

This, fortunately, is not a frequent phenomenon, though it is always possible when we understand the mechanism of its production.

As far back as 1923* I reported two cases of this delayed or latent type of x-ray burns (necrogenic radioactive dermatitis) which deserves more general recognition than it has received.

In one case, a young woman, Miss A. B., 25 years of age, was treated by radiation for a small toxic goiter. The patient was treated cautiously and serially at long intervals by an expert, the treatment being discontinued with the first appearance of an erythematous blush. All x-ray treatment ceased as the patient, after three months of intermittent radiation, was apparently completely recovered and well. At the end of four years of apparent cure and good health, a peculiar progressive dermatitis made its appearance in the neck, extending from the chin to the sternum and, laterally, to the clavicles. Necrotic patches and sloughing areas began to appear along the whole surface of the radiated area, which became very foul with ichorus discharges coincidentally with these local lesions, and the patient began to develop septic symptoms, delirium, fever, and stupor, with loss of vesical and rectal control. The secretions from the slough were particularly offensive. With these evidences of a profound toxic state Dr. S., the attending surgeon, decided after consultation, to excise the entire diseased area, doing this in several sections. The patient immediately began to improve, and by the end of the ninth week was allowed to return home with her mind completely restored. The wound was slow in healing but it finally yielded to extensive and repeated grafting. Seven years after a complete recovery she married and continued well.

In another patient, a widow of 58 years, the outcome was not so favorable. After undergoing a very sweeping mamectomy on Halsted lines she remained apparently well both locally and constitutionally for three years (1903-1907), when a diffuse sloughing dermatitis appeared over the field which had been prophylactically radiated after the operation. The dermatitis appeared in patches, which gradually coalesced, leaving a vast surface of grey putrid skin which on removal left a foul grey area of unhealthy granulations and exudates, and which resisted all efforts at healing, or grafting. A radical extirpation of the entire surface of the left pectoral region was impossible, as it would have necessitated a solid resection of the entire thickness of the chest wall without any available skin flaps to cover the vacant space. This patient died 18 years after the original appearance of the delayed x-ray burn. The history of this patient was one of a long series of complications and vicissitudes, the death caused by prolonged suppuration, inanition, general cachexia, and exhaustion.

[*Added commentaries since the discussion by Dr. Matas:*] The detailed story of this patient was given in a discussion previously referred to in the Am. Surg. Trans. for 1938.

The pathogeny of this type of long-delayed burns was fully explained in a paper by Dr. Karl Grasman of Munich in 1923 (Deutsch Zeitscrift für Chirurgie, **149**: 115, 1923). In this case Grasman reports the appearance of an x-ray ulcerative dermatitis which appeared four years after the patient had fully recovered from a fibro-myoxoma of the uterus which had been treated by x-ray radiation. The necrotic and ulcerated areas in the lower lumbar region and buttocks had resisted all forms of treatment until the diseased necrotic area was totally extirpated. After this was done complete recovery followed, fully confirmed two years after the operation. Professor Duerck, who made a very thorough study of the radiated tissues, determined that the necrotic process was caused by a primary radiogenic proliferation of the vascular endothelium of the arterioles and capillaries of the radiated region, specially affecting the vessels of the derm and

* See R. Matas, Discussion of paper on "X-ray Burns and Their Surgical Treatment" by C. A. Porter, M.D. and S. B. Wolbach, M.D.—in Trans. Am. Surg. Assn., pp. 462-467, Vol. 41, 1923.

subcutaneous connected tissues, leading to a progressive and fatal ischemia and nutritional disturbance of the radiated fields.

In summing up the results of my observations and experience, I need only repeat the conclusions arrived at in the previously quoted paper read at the meeting of this Society at Rochester, Minnesota, in 1923, viz.: "that once an x-ray burn is confirmed and especially if it has advanced to ulceration, practically nothing will accomplish a cure but a total excision of the entire diseased area; that is, provided this can be covered with healthy well-nourished flaps or by grafting provisionally on a perfectly healthy base," and with the proper judgment and skill displayed by Dr. Brown in his exhibit here today.

THE CIRCULATION OF THE SMALL INTESTINE: AN EVALUATION OF ITS REVASCULARIZING POTENTIAL*

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THE BLOOD SUPPLY of the small intestine is not a new field for investigation. Andreas Vesalius,[1] in 1540, presented an interesting, and for that day, surprisingly accurate illustration of the small intestine and its blood vessels† (Fig. 1). Since then our knowledge of the blood vessels of the small intestine has been greatly amplified. Upon a few points which have long awaited clarification, many differences of opinion persist among surgeons. Further, certain erroneous ideas, long since disproved, repeatedly recur in the surgical literature of today. Hence, it seems worthwhile to review briefly some of the more outstanding contributions to this field and to summarize the results of additional investigations carried out in our own laboratories during the past ten years.

The duodenum, obviously a part of the small intestine, has been well studied by Wilmer[2] and will not be considered in this paper which is concerned only with the blood vessels of the jejunum and ileum, that portion of the small intestine which lies between the ligament of Treitz and the ileocecal valve. This area is supplied exclusively by the superior mesenteric artery, a branch of the abdominal aorta, and is drained by the superior mesenteric vein, a tributary of the portal system. For purposes of discussion it is convenient to subdivide the blood vessels of the small intestine into two groups: (1) Those vessels (extra-intestinal) which lie between the wall of the intestine and the superior mesenteric trunks, referred to as the *mesenteric vessels,* and (2) those which lie on or within the wall of the intestine, called *mural vessels.*

Usual descriptions of the mesenteric vessels are in agreement so far as the larger arteries and veins are concerned. This is to be expected, for they are of such size, and are so placed that their demonstration is relatively easy. The vasa recta, and to an even greater extent the vessels within the intestinal wall, present much greater difficulties in study, usually requiring injections and other special technics. As a result many discrepancies are to be found among the descriptions of these finer radicles of the intestinal circulation. This

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† The accompanying text describes the intestinal arteries arising from a large trunk from the aorta, giving off branches which branch in arborescent fashion to communicate with each other within the intestine. Similarly formed veins are described as joining the portal system which leads to the liver.

emphasizes the fact that technic for vascular study must be carefully chosen for suitability to the problem, and the results critically analyzed if one is to avoid the hazard of contributing to misinformation rather than adding to knowledge.

Dwight[3] in 1898 described the human small intestinal vessels before the Association of American Anatomists, and published his findings in somewhat different form in the Anatomische Anzeiger in 1903.[4] This is one of the earliest and best descriptions, brief but accurate, and he clearly recounts the characteristics of the arcuate vessels and observes that the vasa recta do not intercommunicate between their origin and the point where they join the intestinal wall. The classical papers of Monks[5-7] are familiar to all surgeons, and added greatly to understanding of the increasing complexity of the arcuate system and greater amounts of fat in the mesentery in the distal portions of the intestine. Eisberg[8] reported a most complete study of the small intestinal circulation in both man and the dog, and Cokkinis[9, 10] presented detailed findings based upon injection studies of human intestines.

FIG. 1.—The small intestine and its circulation as portrayed by Andreas Vesalius in 1543.[1]

Comparative studies of the small intestinal circulation were reported by Mall[11] who presented a thorough study of the dog with particular attention paid to the finer ramifications; by Bradley[12] who gave a brief but accurate account of the mesenteric vessels of the dog; and by De Blasi[13] who compared the branches of the superior mesenteric artery of dog and man, believing the latter to be better suited for efficient revascularization. Dieulafé[14] used radiopaque media for comparing the mesenteric vessels of the dog and rabbit. Morton[15] published a most interesting comparison of the relative vascularity of the duodenum and ileum of the dog. Latarjet and Forgeot[16] described the jejunal and ileal circulation of man, dog, cat, horse, pig and rabbit. One of us (Noer[17]) presented a detailed comparative study of the small intestinal circulation of man and certain laboratory animals. Much of this work is summarized later in this paper, as essential background.

Experimental mesenteric occlusion, a most useful technic for studying collateral circulation, has formed the basis for considerable investigation. The

literature covering this phase of the problem was reviewed in a previous publication on this subject by Derr and Noer[18] and will not be considered again at this time. Similarly, references to previous work on the effect of distention upon blood flow through the intestinal wall may be found in the paper on this subject by Noer and Derr.[19]

TECHNICS

Anatomical studies of the blood vessels of the jejunum and ileum reported in 1943[17] were based upon five human autopsy specimens and 29 specimens of 14 species of animals. Since then additional injections have been made in three rabbits, three dogs, two rats and two hamsters. Further, careful check upon the accuracy of the human findings has been made during the course of revascularization studies of 29 loops of human intestine. Thus the morphological descriptions detailed in this paper are based upon observation of 34 human autopsy specimens, nine dogs, five rabbits and 26 other animals.

Injection technics have formed the basis for conclusions as to morphology. Our earliest studies utilized the celloidin injection and corrosion technic described by Hinman, Morison and Lee-Brown.[20] This provided excellent demonstration of the intestinal vessels, but the relationship of the vessels to the intestinal wall is not shown, so we rather early changed to the use of clearing technics after the method of Spalteholz.[21] Liquid latex, as described by Batson,[22] proved to be an ideal medium for this. A modified combination of the technics of Batson and Spalteholz was described in detail in the 1943 publication.[17] The findings in cleared specimens in that report were checked by radiopaque injections of bismuth oxychloride after the method of Hill.[23, 24] More recently specimens have been cleared in uncatalyzed polystyrene, then embedded in catalyzed polystyrene, cured by heat. This results in the most satisfactory method which we have yet encountered. The transparent plastic mounts are permanent, nearly unbreakable, and provide specimens equally suited to gross or microscopic study.

Mesenteric occlusion experiments were carried out in dogs.[18] Three types of ligation were practised: (1) Intestinal arteries alone, in varying number, (2) arteries, veins and nerves, and (3) veins alone. Ligation in continuity was done in 38 dogs, but because of doubt as to completeness of interruption all experiments were repeated with double ligation and division in a total of 83 additional dogs. Autopsies demonstrated the results in dogs which succumbed, and those which survived were sacrificed for autopsy after 10 days.

For further investigation of the mode of revascularization India ink in bovine plasma was injected in additional dogs after selected ligations as above, and the findings recorded by slow motion cine-photography.[25] The India ink in bovine plasma was chosen because its viscosity and particulate size approximates that of blood, because its osmotic pressure is such that edema and diffusion from the vessels does not occur, and because its blackness is ideally suited for recording by cine-photography the course taken by the medium. A close correlation was demonstrated between the length of loop which the animal

would survive in life and that which could be filled by injection. As a result it was felt justifiable to use this approach for a study of revascularization in human autopsy material. In all, nine human loops were studied, together with 20 dog loops, 15 from the rabbit and seven from the opossum.

The effect of distention on the efficiency of the anastomotic mechanisms was studied by similar experiments after introduction of balloons into the intestine. Intraluminal pressures were recorded with mercury manometers, and were varied during the course of injection while results were recorded for repeated study by slow motion cine-photography. A total of 20 human autopsy specimens were utilized for this phase of the investigation.[19]

It occurred to us that a natural extension of this work would be the use of "Roux-Y" loops for determination of the degree of mobility possible with

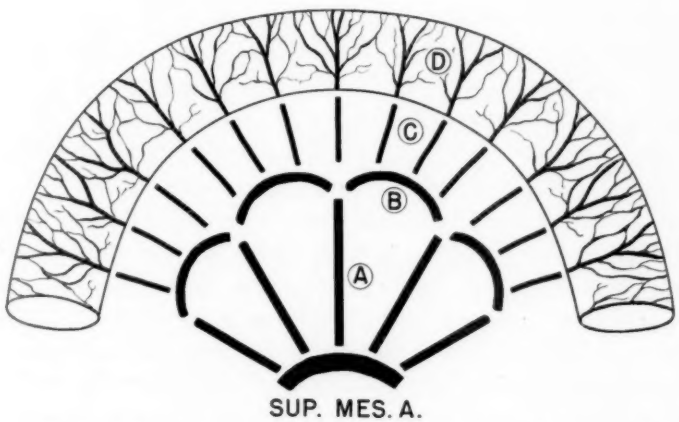

FIG. 2.—Basic pattern of the small intestinal circulation. A. Intestinal vessels; B. Arcuate vessels; C. Vasa recta; D. Mural trunks and anastomoses.

this procedure. It soon developed that this approach might also provide additional information as to the effects of distention upon partially devascularized intestine. The technic and results are detailed later in this paper.

RESULTS

Detailed analysis of the comparative morphologic findings appears in the 1943 report.[17] Since then additional animals have been injected and many of the original specimens have been carefully re-studied with the aid of a binocular microscope with particular attention paid to the finer ramifications within the intestinal wall. Hence it appears desirable to restate some of these findings with slight changes in the finer details as viewed in the light of our subsequent studies.

The basic pattern of the small intestinal circulation is illustrated diagrammatically in Fig. 2. All species conform to this basic plan though individual

variations are pronounced and at times even extreme as in the case of the pig. The superior mesenteric artery gives rise to a series of intestinal arteries which are joined by vessels which form the arcuate system. From the most peripheral of these arcades arise the vasa recta, smaller and shorter vessels which pass to the intestinal wall. Upon reaching the latter, they pass either to one side or the other of the intestine or bifurcate to send a branch to both sides. These vessels, now called mural trunks, pass into the wall of the intestine where they branch and anastomose freely with one another in a manner varying according to species. It is thus apparent that there are two principal anastomotic routes: (1) The arcuate system, and (2) the intramural anastomoses.

In man (Fig. 3 a and b) the intestinal vessels vary in number between 12 and 16. The arches, simple and primary in the upper jejunum, increase in complexity in the more distal portions of the gut so that secondary, tertiary, quaternary and even quinary loops may be demonstrated. The vasa recta arise from the most peripheral arcades, and never intercommunicate between the peripheral arcade and the intestinal wall. Once the latter has been reached, however, the intercommunications between the mural trunks are abundant, in the jejunum and upper ileum by way of direct intercommunications passing obliquely along the wall, and in the lower ileum by a free plexiform type of anastomosis (See discussion of intramural anastomoses below).

The dog (Fig. 3 c and d) presents a pattern varying considerably from this. Here the arcades are large, seldom become more than secondary or at the most tertiary and, for the most part, lie in close proximity to the intestinal wall. As a result the vasa recta are short and unlike those of man they abundantly intercommunicate, producing a free mesenteric border arterial anastomosis—a situation which does not exist in man. The intestinal wall of the dog is rather thick but the mural vessels show much fewer direct intercommunications than is the case in man, the majority of intramural anastomoses being through a plexiform type of intercommunication.

The dog has been described in some detail because of its considerable difference from the human pattern and because of its frequent use as an experimental animal. Other species have been described in the report mentioned above and it does not seem appropriate to include details in this paper. It is worthy of note, however, that most species show a resemblance to either the human or the canine pattern of mesenteric vascular morphology. Table I lists, by common name, the species which fall into these various patterns (See also Fig. 4).

The anastomoses within the intestinal wall tend to be characteristic of species. Figure 5 shows the three types of intramural anastomosis most frequently seen (See also Figs. 3 and 4). Type A, direct intercommunication between mural trunks by good-sized oblique vessels is characteristic of man, particularly in the jejunum and upper ileum. Type B in which the mural vessels break up into plexuses which then intercommunicate by much smaller anastomoses, is characteristic of the dog and of the terminal ileum of man. Type C shows arching intercommunicating vessels passing between the mural

trunks in an axis parallel to the long axis of the intestine. This pattern is characteristic of the rabbit, to a lesser extent of the opossum and reaches its highest degree of development in the rat.

The mesenteric occlusion experiments carried out in the dog[18] revealed several interesting facts with reference to the ability of this animal's jejunum and ileum to withstand circulatory interruption. Contrary to previous reports, in this series interruption of any or all of the mesenteric supply to a 15 cm. segment of dog's small intestine resulted in death of less than half the animals so treated. Also, contrary to the usual assumption, the venous ligations produced no higher mortality than interruption of any other vessel or combination of vessels. It was further shown that in this animal complete vascular deprivation of a segment 15 cm. or less in length could not be accomplished uniformly by interruption of intestinal and arcuate vessels. This was considered presump-

TABLE I.—*Comparative Classification of the Jejunal and Ileal Vascular Patterns*

"Human" Pattern[1]	"Canine" Pattern[2]	Others[3]
Man	Dog	Pig
Chimpanzee	Cat	Marmot
Opossum	Rhesus monkey	Sheep
Rabbit*	Raccoon	Goat
Wallaroo	Guinea pig	Rat
Hamster	Red fox	

[1] *"Human" pattern:* Well developed arcuate vessels, relatively long vasa recta which do not intercommunicate, mural vessels joined for the most part by good-sized oblique vascular branches.
[2] *"Canine" pattern*: Relatively simple mesenteric arches which lie adjacent to the intestinal wall, short vasa recta which abundantly intercommunicate, mural trunks joined by plexiform anastomoses.
[3] *Other patterns*; Jejunal and ileal vessels intermediate between "human" and "canine" types (marmot and rat) or differing in marked degree from both (pig, sheep, goat).

* The rabbit shows occasional failure to complete its mesenteric arcades (Fig. 4), hence has a less efficient revascularizing potential in these areas.

tive evidence that some revascularization must occur by way of the intramural anastomoses. This study further showed no significant difference between the revascularizing potential of different levels of the small intestine.

Additional studies[25] were undertaken in an effort to determine the exact means by which revascularization took place following mesenteric interruption. It was shown that there is a close correlation between the degree of vascular deprivation which dogs can survive and the amount of intestine which can successfully be filled by injection under similar circumstances. It thus appeared that injection technics might provide a suitable means for investigating revascularizing ability not only in the dog but also in man where ligation and survival experiments are obviously impossible. These studies revealed that approximately 15 cm. is the maximum length of intestine which can successfully be filled with injection media after mesenteric vascular deprivation. Division of intestinal arteries alone resulted in filling of the interrupted arcuate

system from adjacent intact intestinal arteries. When interruption of the arcuate system at either extremity of the loop was added to division of the intestinal arteries, filling took place by way of vessels *within the intestinal wall,*

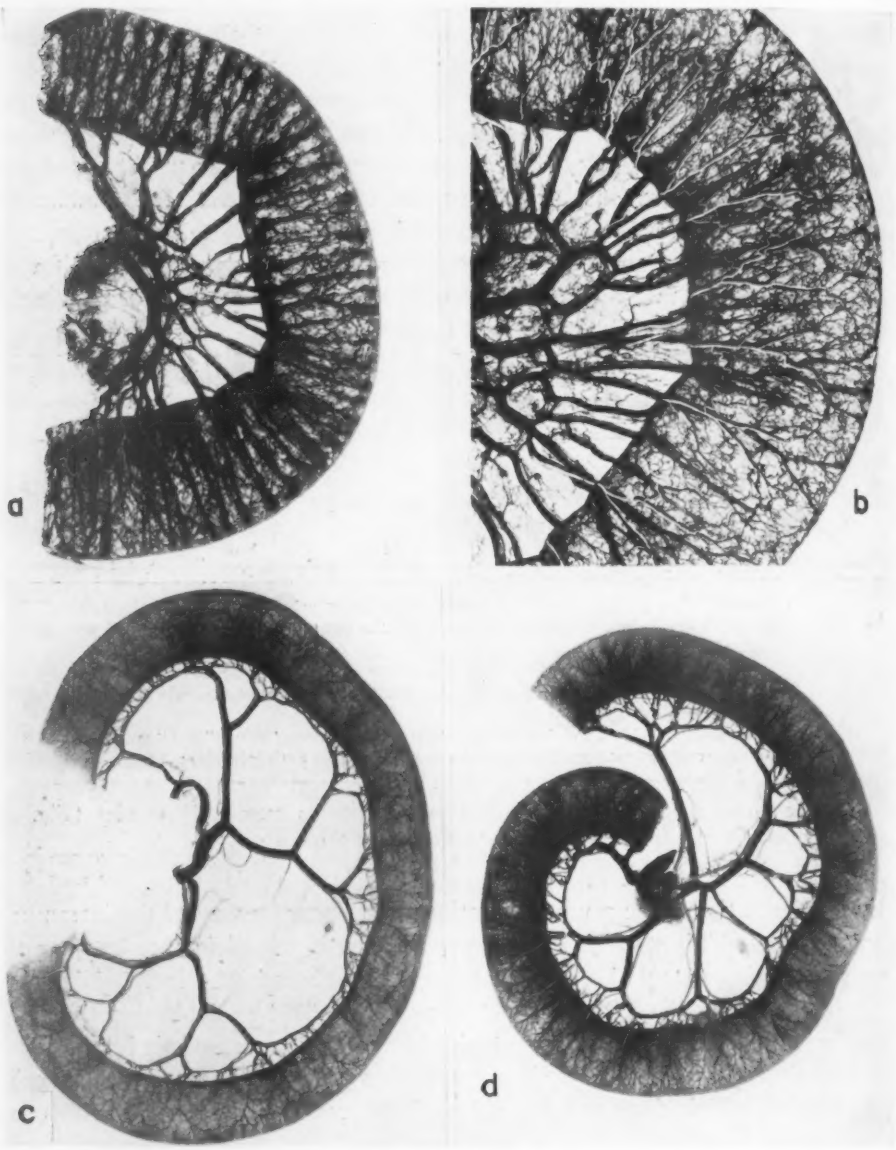

FIG. 3.—Photographs of latex injected and cleared loops of intestine. A. Human jejunum; B. Close-up of human ileum; C. Dog jejunum; D. Dog ileum.

thence through the vasa recta into the isolated arcuate system and thence to the remainder of the loop through this arcuate system and its vasa recta. Surprisingly enough, interruption of the intestinal arteries and arcuate vessels

plus all of the vasa recta to the loop under study was followed by filling of the entire loop by way of the intramural vessels and their anastomoses. This occurred with complete regularity in man, opossum and rabbit. Only in the

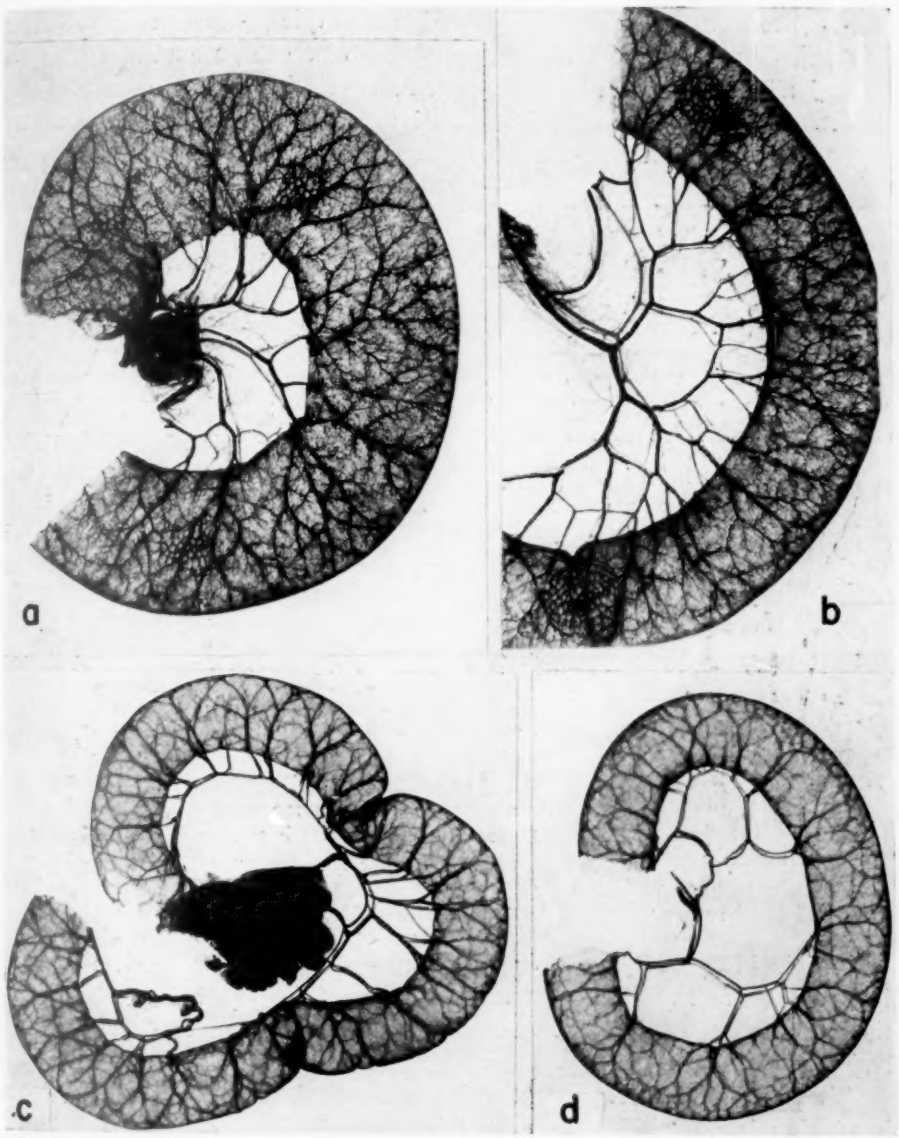

FIG. 4.—Photographs of latex injected and cleared loops of intestine. A. Opossum jejunum; B. Opossum terminal ileum; C. Rabbit jejunum; D. Rabbit ileum.

dog did 15 cm. loops occasionally fail of complete filling in their central portion. It was felt that this situation might be explained by the type of intramural anastomosis present in this animal, and it was this finding more than any other

which stimulated our re-study of the intramural anastomoses mentioned under morphologic findings.

These results raised the question as to the possible influence which distention might have upon this revascularizing potential. The experiments just referred to were repeated after production of varying degrees of intraluminal distention[19] and it was shown that pressures of 60 to 70 mm. mercury prevented all intramural filling by injection, even with the mesenteric system intact. Filling of the larger intramural vessels occurred at 40 to 20 mm. mercury but complete vascular filling occurred only in the absence of distention.

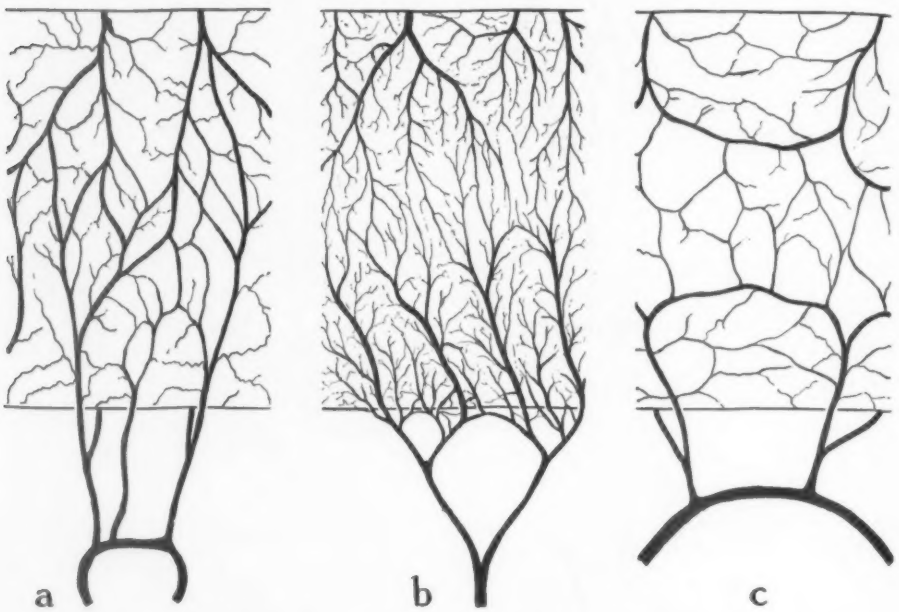

FIG. 5.—Types of intramural anastomoses (see also Figs. 3 and 4). A. Direct communications between mural trunks, e.g., man. B. "Plexiform" type of anastomosis, e.g., dog. C. Arching type of intercommunication, e.g., rabbit, rat.

In intestinal loops subjected to complete mesenteric vascular deprivation (*i.e.*, interruption of all vasa recta to the loop), filling of the deprived area by way of the intramural anastomoses could not be obtained until complete decompression had been accomplished.

"Roux-Y" experiments, not previously reported, have produced additional interesting data. Fig. 6 is a diagrammatic representation of the procedure in the first series. The small bowel was transected 5 to 10 cm. beyond the ligament of Treitz, and the distal end closed with a double layer of sutures. A 15 to 25 cm. segment of intestine immediately distal to the point of transection was then freed by dividing the mesentery near its root but preserving its arcuate system. The proximal cut end was then anastomosed to the jejunum at the distal end of the free segment resulting in a typical "Roux-Y" loop, closed at its free

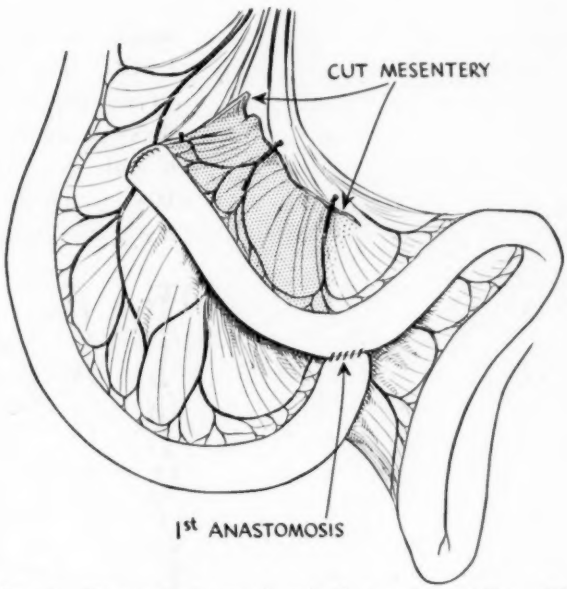

FIG. 6.—Diagram of procedure in first series of "Roux-Y" experiments.

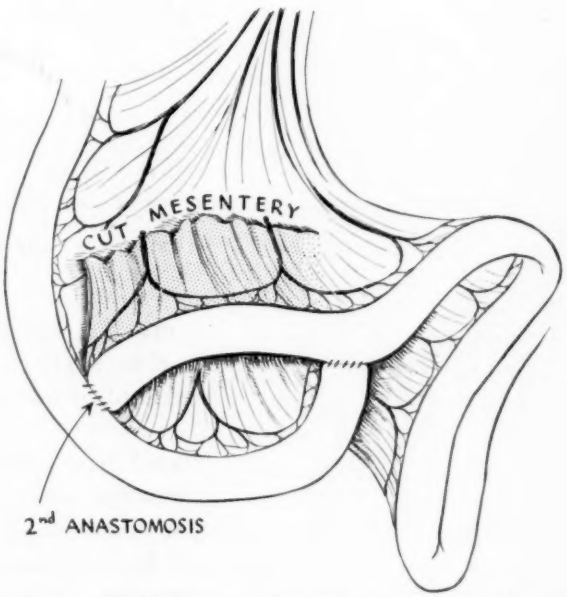

FIG. 7.—Diagram of procedure in second series of "Roux-Y" experiments (addition of proximal entero-enterostomy).

end. Seven dogs were subjected to this procedure. Postoperatively all of these animals were severely ill, and all but one of them died within one to six days. Postmortem examinations revealed the free loops to be dilated, gangrenous, and in most instances perforated. One animal with a 25 cm. loop survived after an extremely stormy postoperative course.

The procedure in the second series of seven dogs is represented in Fig. 7. Here, in addition to the "Roux-Y," a proximal end-to-side entero-enterostomy was also performed to vent the free loop into the intestine. One animal with a 25 cm. loop died on the first postoperative day. Postmortem examination revealed no dilatation but a 3 cm. area of infarction and perforation at the proximal end of the distal segment. The remaining animals showed very little postoperative reaction, remaining alert and undistended, with good appetites. They were sacrificed for autopsy approximately one month after operation. The loop of gut in question was of comparable appearance to the remaining intestine, and the anastomoses were patent. There was no evidence of distention.

In summary, six of seven dogs in whom a "Roux-Y" anastomosis with a blind segment was performed died in from one to six days postoperatively with loops which showed dilatation, gangrene, and perforation. The single animal which survived did so only after a protracted stormy postoperative course. In contrast, six of seven dogs in whom the loop was decompressed by a proximal entero-enterostomy survived, and reoperation revealed the loops to be normal in appearance (See Fig. 8).

DISCUSSION

The morphologic studies have clarified our understanding of the vascular pattern in the jejunum and ileum of man, and we hope they may correct some of the discrepancies to be found in the literature. The comparative material has been briefly reviewed because of our firm conviction that too little attention is paid to species peculiarities in the choice of experimental animals. There is far too widespread a tendency to select animals on the basis of convenience to the investigator rather than upon suitability of a given species to the proposed investigation. The almost universal selection of the dog for experimental work upon intestinal obstruction and its circulatory disturbances is an outstanding example of this point. The mesenteric circulation of this animal is perhaps somewhat more abundant than that of man from whose pattern it differs markedly. The intramural circulation, on the other hand, appears to be definitely less efficient to such an extent as to require considerable care in the interpretation of results obtained from the use of this animal. The opossum and the more readily available rabbit both resemble man far more closely with respect to both the mesenteric pattern and the intramural vessels. Our subsequent studies herein reviewed thus lend further weight to one of the statements expressed in our 1943 paper: "These conclusions emphasize the fact that if findings are to be applied to man the experimental animals should be chosen only after careful investigation has shown a somewhat similar morphologic

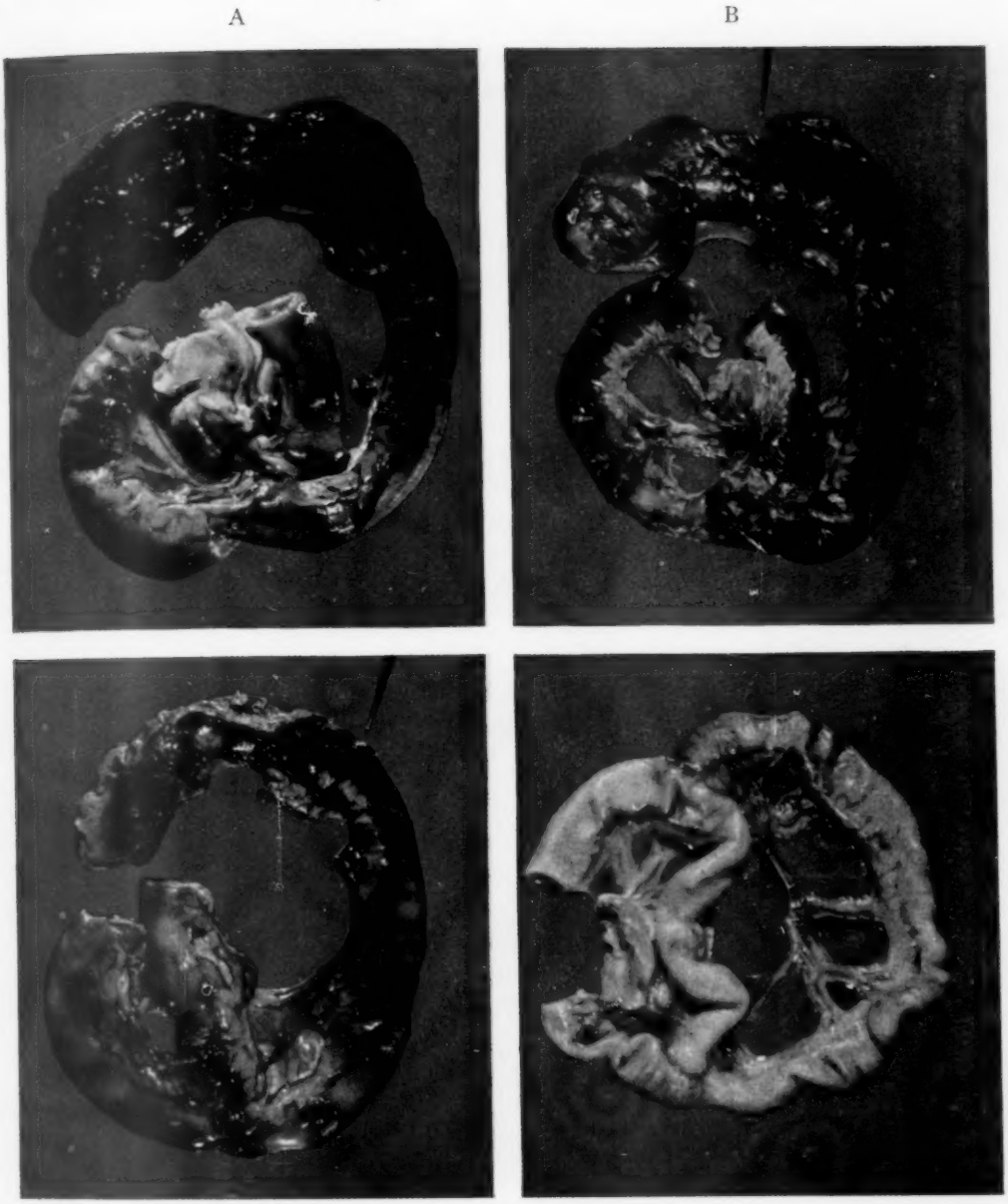

FIG. 8.—Postmortem specimens obtained after two types of "Roux-Y" experiments. A. Specimen, Series I, showing dilatation and hemorrhagic necrosis of the free loop, without perforation. B. Specimen, Series I, showing dilatation, necrosis and perforation of free loop. (Pointer indicates site of perforation.) C. Specimen, Series I, showing necrosis with perforation at site indicated by pointer. D. Specimen, Series II. Note absence of distention and normal appearance of loop. (Animal living and well, sacrificed for autopsy.)

and physiologic relationship. Ideally the animals should also be of known age and strain and should be vigorous and free from disease."

The morphologic studies, coupled with the other data here presented, emphasize the great vascular reserve of the jejunum and ileum. It is apparent that there are two principal anastomotic routes, one in the arcuate system, the other within the intestinal wall. It has been generally assumed that the former is the only mechanism which can be uniformly counted upon; in fact, this has been considered so important that it is common surgical teaching that not more than 2 cm. of intestine can be safely denuded of its mesenteric vessels. These studies indicate a much greater degree of importance of the intramural anastomotic system than had previously been supposed; these anastomoses apparently can compensate for rather large losses of mesenteric vessels. It is interesting in this connection to note clinical reports of recovery following traumatic severance of several inches of the mesenteric supply.[26] Survival in these cases was attributed to blood supply developed from omentum wrapped about the loops at operation. While such may have taken place, our studies would indicate that actually it was probably the efficiency of the intramural anastomoses which maintained the viability of the intestine. It would be a mistake to consider that our findings justify any radical changes in the technic of intestinal anastomosis for one obviously ought to preserve all of the blood supply possible. Nevertheless, we feel that these findings may afford considerable reassurance when circumstances demand greater dependence upon the intramural anastomoses than we had previously thought compatible with survival.

The deleterious effect of distention upon intestinal revascularization might have been predicted but it proved to be greater than we had anticipated. Operative findings and autopsy specimens have frequently indicated that extreme degrees of distention produce sufficient avascularity to cause pressure necrosis and intestinal perforation. Thus the ability to prevent filling by marked distention was no surprise. The degree of vascular interference caused by moderate degrees of distention, however, was greater than anticipated. This finding emphasizes the need for complete intestinal decompression in all conditions associated with intestinal distention. Further, the results indicate a need for constant decompression wherever the integrity of the intestinal lumen is threatened by injury or operative trauma. Therein may lie the explanation for failure of suture lines thought to be adequate but later giving way due to partial avascularity produced by moderate distention.

Loops with proximal closed ends somewhat similar to those used in "Roux-Y" anastomoses were chosen for study because they provided (1) vascularization from one end instead of two, and (2) because they were of sufficient length to permit of moderate distention at the free end. When the closed end was vented into the intestine so that the portion farthest from the source of blood supply would be decompressed, necrosis was less likely to occur. While our primary intent was not that of testing the "Roux-Y" type of anasto-

mosis in regard to the integrity of the blood supply, it must be pointed out that our studies do confirm the concept that anastomoses by use of loops are safer from a vascular standpoint since they have blood supply at both ends. This is especially so if the loops are kept decompressed by means of an entero-enterostomy.

CONCLUSIONS

1. Morphologic and physiologic experiments indicate that there are two principal routes for revascularization in the jejunum and ileum: (1) The arcuate system of mesenteric vessels, and (2) the anastomoses within the intestinal wall.

2. So long as the arcuate system remains intact it provides a most efficient compensatory mechanism, but when it fails to function the intramural vessels are probably far more effective than hitherto supposed. These vessels alone appear able to nourish several centimeters of jejunum or ileum.

3. Species differences are great both with respect to the mesenteric pattern and the type of intramural anastomosis. These factors should be carefully considered in the selection of experimental animals for investigations referable to man.

4. Distention in any degree produces definite interference with the efficiency of the intramural anastomotic mechanism of the small intestine.

Dr. Gordon H. Scott, Professor of Anatomy, has made many helpful suggestions during the course of these investigations.

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DISCUSSION.—DR. JACOB FINE, Brookline, Mass.: I would like to call your attention to an experiment done on dogs several years ago by one of my colleagues and myself, in which we obstructed the venous return of loops of small intestine about ten inches long in the dog, with the finding that in every instance when nothing else was done, death from gangrene and peritonitis occurred within 24 hours or less; but that if an antibiotic were placed in that loop a recovery of viability and a return of function took place almost uniformly. Distention was not an important factor in these results.

I think it is important to stress the fact that viability of a loop of gut with deficient blood supply is conditioned by local bacterial action as well as by the degree of vascular impairment.

HERPES ZOSTER: A SURGICAL PROCEDURE FOR THE TREATMENT OF POSTHERPETIC NEURALGIA*

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Numerous studies of material derived from postmortem examination of patients who had manifested clinical features of herpes zoster have shown outstanding pathological lesions in one or more dorsal root ganglia. Associated processes in the spinal cord, the posterior roots, the peripheral nerves, and the dermatomic zone of skin subserved by the implicated ganglion or ganglia have been equally well authenticated. Also there are many recordings concerning the clinical aspect of the disorder. Certainly the available elaborate descriptions of the changing skin eruption during the acute phase of the disease leaves little to be added. In attempting to correlate these clinical and pathological observations, especially the problem of the pathophysiological mechanism that produces postherpetic neuralgia, one finds oneself on less secure ground. It has been implied, and seemingly with quite general acceptance, that the obvious changes in the dorsal root ganglion are in some manner responsible for the alterations in afferent pathways, and hence the pain. Possibly this is true; however, we have made observations that have prompted us to question the validity of this deduction. From an over-all consideration of the subject, we have evolved a therapeutic approach for postherpetic neuralgia different from those previously employed, namely, excision of the involved skin and subcutaneous tissue.

THE CLINICAL PICTURE

There appears to be a general belief that herpes zoster is a disease that affects the aged and debilitated. While it may occur at any age, there are seldom enduring sequelae among those afflicted before the fourth decade of life. There is no available knowledge relative to the portal of entry of the infectious agent, and the early systemic responses—mild fever, general malaise and "muscle ache"—offer no clue as to the manner of invasion. It is only after the appearance of a cutaneous erythema, with scattered small vesicles distributed in a dermatomic fashion, that the clinician becomes certain of the nature of the disease. Concomitant with, or at times just preceding the development of the rash, the patient's attention is attracted to the affected part by an increased sensitivity of the segment of skin that is becoming involved. Shortly after the appearance of the erythematous rash the hypersensitive cutaneous area takes on a burning discomfort which is commonly aggravated even by the pressure of light clothing. Added to this discomfort are intermittent

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spells of sharp stabbing pain, sometimes described as extending through the part affected, whereas in other instances the pain tends to follow the surface of the dermatome implicated. During the second week of illness, blebs appear. In mild cases, these are small and separate but with varying degrees of elevation of erythematous skin between them. Only a part of the dermatome, about the size of one's hand, may show the cutaneous lesion. In such cases, if the involvement is thoracic, the blebs may be situated paravertebrally or, less frequently, anteriorly. Under these conditions, even though the remaining portion of the dermatome manifests no visible lesion one may demonstrate by appropriate stimuli that the sensory receptors of the entire segment are altered.

In severe cases, the erythema covers the full extent of the dermatome, the blebs are larger and tend to coalesce, the burning discomfort is continuous, and any movement that changes the tension of the skin of the area precipitates sharp stabs of pain. The patient becomes distraught with the constant day and night discomfort. Medication, regardless of its potency, offers only temporary relief.

In the majority of instances, the erythema begins to recede during the third week. The blebs show crusting and wrinkling, and scattered small open wounds resulting from rupture of some of the blebs may be present. Both the drawing, burning discomfort and the recurring sharp pain become less disturbing. By the fifth to sixth week, the scales of the encrusted blebs have fallen away, leaving bizarre-shaped pink scars. The previously erythematous areas not implicated by the blisters take on a light brownish hue. Gradually the scars retract, thereby producing pocks devoid of pigment. The end result is an irregular-shaped tongue of skin, within the confines of a dermatome, mottled by pigmentation and freckled with pocks lacking in normal pigment. For a time, the area remains mildly "tender" to rubbing, but this slowly subsides and by the end of two or three months the patient has recovered symptomatically. Cutaneous evidence of the disease usually remains for years.

Other patients do not fare so well. The coalescing blebs often rupture if not well protected from external pressure, and a large part of the dermatome becomes covered with a weeping crust. The long continued twisting, burning pain resulting in sleepless nights may lead to an abnormal psychologic state. Patients so afflicted not infrequently speak of suicide as the only way out of their torment. In truth, one who came under our observation was admitted to the hospital following a leap from a third story window, and died shortly thereafter. In some instances, especially in older patients, desquamation and re-formation of crusts over the herpetic area may continue for as long as ten months.

Although the burning and intermittent sharp shooting type of pain may persist for months, or even years, after the acute phase of a relatively mild attack of shingles, this occurs only in exceptional instances. More commonly, the so-called postherpetic neuralgia is encountered in the fifth, sixth or seventh

decade of life, and usually follows a severe attack of zoster. At all events, postherpetic neuralgia is a well established clinical entity that may be a continuation of or, more infrequently, a sequel of herpes zoster. It is with this complication of zoster involving the trunk and extremities that this presentation is chiefly concerned.

In postherpetic neuralgia, the outstanding complaint is variously described by the patients as twisting, burning, drawing, boring, pressing or sharp shooting. The pain is usually limited to the zone of pocked and bronzed skin of a single dermatome. In one case in our experience the sharp stabs of pain were referable to dermatomic segments caudad to the ones bearing the overt scars of the acute attack. By the time the patient comes under the observation of the surgeon, many forms of physical and medicinal therapy have been tried with little if any beneficial effect. Examination discloses the obvious zone of skin involved. As is often observed in patients with long-standing discomfort of a part, the results of detailed sensory examination are not wholly reliable. In some patients with zoster even the slightest superficial pressure is said to cause a burning pain. Since certain alterations in cutaneous sensations have been demonstrated sufficiently often in the same patients, and these changes have been essentially the same from case to case, one can be reasonably sure that they are dependent upon organic changes and should not be attributed to an abnormal psychological trait. By lightly drawing a sharp object over the normal and onto the abnormal skin, the dermatome involved may be delineated. Within this zone, touch is usually blunted or absent. Over the scars touch is not appreciated, whereas the bronzed or relatively normal-appearing skin is hypesthetic. Pin prick as well as excessive degrees of heat and cold, used as stimuli, produce a spreading burning pain. Two-point discrimination seems impaired; however, the application of the points frequently produces a burning sensation, thereby making this interpretation questionable. In all events, the findings resemble those that result from a partial physiologic interruption of a peripheral nerve.

PATHOLOGIC CONSIDERATIONS

The infectious viral nature of the disease is generally assumed. As early as 1861, von Bärensprung,[2] by means of little more than naked-eye postmortem examination, recognized that swelling of a dorsal root ganglion was associated with the cutaneous lesion known to several generations as "zona." On the basis of a most meticulous analysis of postmortem material in 21 cases, Head and Campbell,[1] in 1900, published a classical discourse on the pathological lesions, not only of the skin and dorsal ganglia, but also of the dorsal roots, the spinal cord and peripheral nerves. A host of subsequent reports have amplified their observations.

The inflammatory and degenerative changes in the ganglia, nerve trunks, spinal cord, and skin that characterize the active phase of the disease eventually give way to scarring not dissimilar to that encountered in the end stages of other inflammatory processes. The pathogenesis of the complication known as

postherpetic neuralgia might logically be attributed to these anatomical alterations, but its occurrence in only occasional cases is difficult to explain.

Information concerning the late pathological changes in the skin, especially those pertaining to the fate of cutaneous sensory receptors, seems rather incomplete. The surgical procedure herein reported afforded specimens of skin

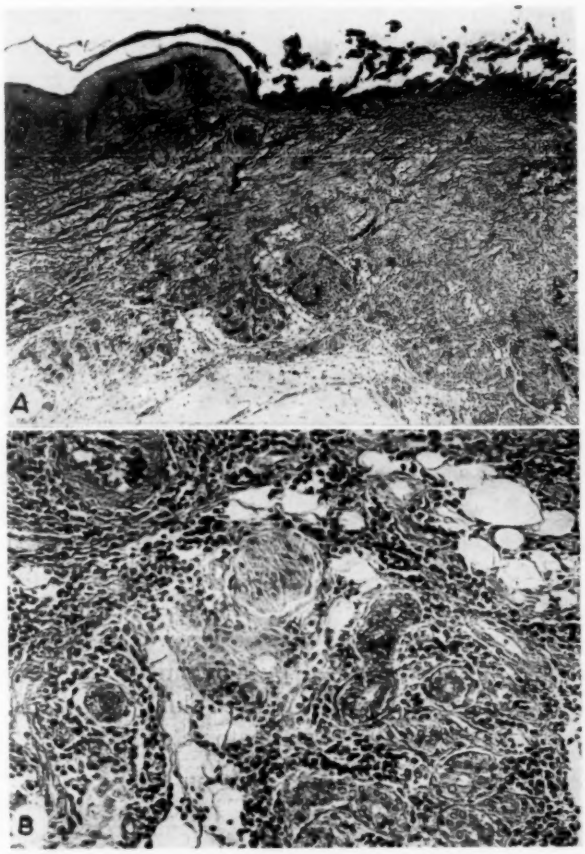

FIG. 1.—Skin and subcutaneous tissue from an active case of herpes zoster, of 41 days' duration, obtained at autopsy. (A) An encrusted ulcer is shown above and to the right. Heavy cellular infiltration involves the entire derma and extends into the subcutaneous area. (B) Subcutaneous glands, blood vessels and nerves are shown surrounded by leukocytes which are predominantly plasma cells.

from patients suffering from postherpetic neuralgia which were removed after varying intervals following the disappearance of the rash. Other specimens obtained at autopsy supplemented this material.

The early lesions in the skin consist histologically of eruptions characterized by vesicles not unlike those of herpes simplex and herpes progenitalis. These

are acute inflammatory lesions manifesting local hyperemia and exudation of fluid into interstices under and among the deeper epithelial cells, and resulting in the formation of blebs covered by the more superficial layers of cells. The epidermal cells undergo both proliferative and degenerative changes, the most striking of which are the appearance of intranuclear inclusion bodies. Leukocytes, consisting largely of plasma cells, accumulate in large numbers in the underlying derma and, in company with polymorphonuclear leukocytes, make their appearance among the disordered epithelial cells and in the fluid within the vesicles. The latter, whether they rupture or not, become crusted over and the area involved eventually becomes healed by fibrosis with re-epithelialization of the surface. It is the site of the healed vesicular lesion that is represented by a white scar that remains visible for years after the subsidence of the acute process.

In addition to the more obvious superficial lesions, the skin is the seat of varying degrees of diffuse inflammatory infiltration involving all levels of the corium and extending into the subcutaneous tissues. There is a marked tendency for the aggregation of leukocytes in masses about the blood vessels and nerves, and even about the hair follicles, sebaceous and sweat glands. In a patient who had been driven to suicide by 41 days of severe pain of herpes, we found occasional small ulcers with crusted surfaces, each lined by a zone of seminecrotic tissue heavily infiltrated with polymorphonuclear leukocytes (Fig. 1A). In the adjacent "live" tissue, the infiltration was predominantly plasmacellular, but included scattered neurophilic and occasional eosinophilic polymorphonuclear cells (Fig. 1B). Numerous focal collections, chiefly of plasma cells, were present in closely-spaced foci within the derma and subcutaneous tissues. Within these lesions many nerves were visible. Occasionally an isolated nerve was seen surrounded by a mantle of plasma cells. Only very few lymphocytes were found in the involved skin in this case. The dorsal root ganglion subserving the implicated dermatome and also the ganglia adjacent and on the opposite side showed heavy infiltration with leukocytes of the same types and in about the same proportions as those found in the skin. These lesions were interpreted as representing a chronic active phase of the inflammatory disease.

Study of the excised skin from a patient in whom the acute manifestations of herpes had subsided about 100 days before, revealed a remarkable degree of persistence of inflammation but, in addition, numerous small densely collagenous scars. The infiltrating cells were composed chiefly of plasma cells, but included a good many lymphocytes. No polymorphonuclear cells were present. The aggregations of cells were more compact than in the case cited above, and there was no diffuse inflammatory infiltration. The scars were occasionally situated deeply within the derma and subcutaneous tissue (Fig. 2A). More frequently, they could be followed inward from the surface as wedge-shaped or fusiform scars suggestive of small neuromas (Fig. 2B). One dermal lesion located about a blood vessel presented a tubercle-like structure and contained

giant cells of foreign-body type (Fig. 3 A). Another focus had become ossified, containing a central cellular island in which giant cells of osteoclastic type were evidently associated with the production of marrow within this focus of metaplastic bone formation (Fig. 3B). The lesions in this case were considered to represent an example of severe skin involvement in a stage of the disease in

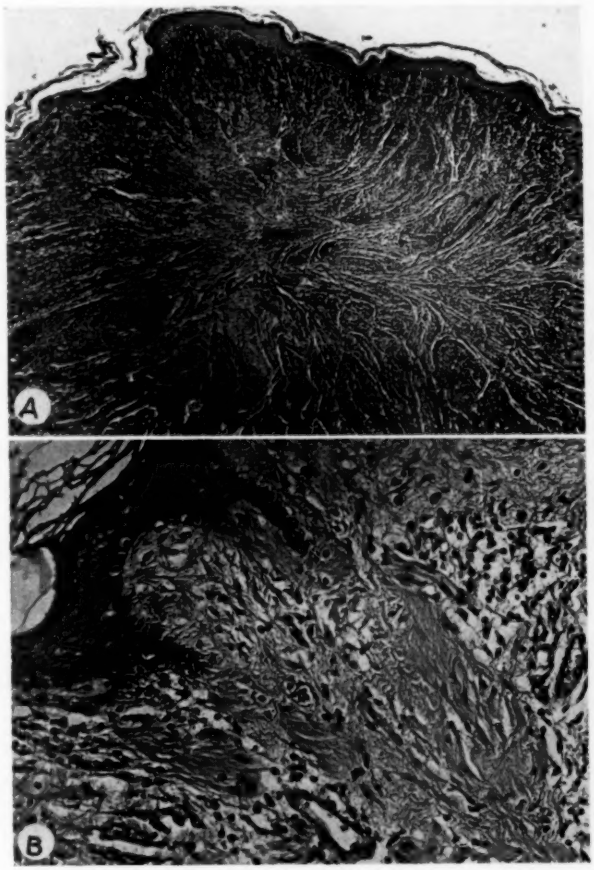

FIG. 2.—Skin surgically excised for relief of postherpetic neuralgia. (A) A deep-seated radial scar with overlying atrophic epidermis. (B) A fusiform scar extending inward from the epidermal surface at a site of puckering. Clusters of plasma cells and lymphocytes are still present 100 days after clinical subsidence of the acute phase.

which advanced healing and persisting active inflammation of subacute type were simultaneously present. Postherpetic neuralgia had been severe until surgical excision relieved the condition.

Still another type of pathologic picture was presented in skin from a woman who died of myocardial infarction 34 months after the onset of herpes and 32 months following the subsidence of clinical evidence of activity in the involved dermatome. This patient showed inconspicuous widely scattered foci

of cellular infiltration, and the cells were almost entirely small lymphocytes. Only small compact scars were present and were situated chiefly within the derma. This case was classified as representing the end or healed stage of herpes.

In all of the cases studied, atrophy and distortion of the epidermis, with abnormalities of pigmentation, were encountered.

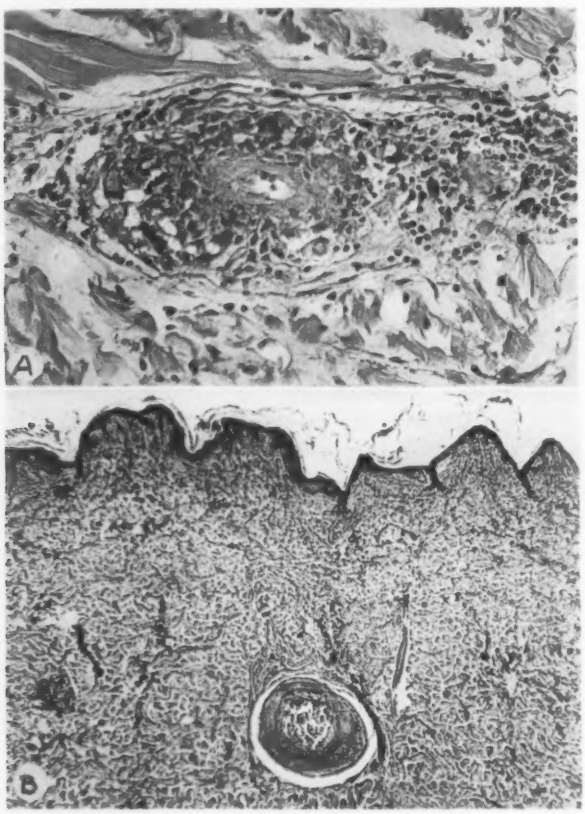

FIG. 3.—(A) Tubercle-like dermal nodule formed about a blood vessel. Giant cells of foreign-body type are evident. (B) An island of bone interpreted as the result of metaplasia in a scar is situated beneath the atrophic distorted epidermis. Hair follicles and sebaceous glands are absent.

It would seem logical to assume that the implication of nervous structures within inflammatory cutaneous foci in all phases of the disease might be responsible for the persistence of pain and other sensory disturbances encountered in those who suffer from "postherpetic neuralgia."

SURGICAL EXPERIENCES

In view of the debilitation that results from postherpetic neuralgia, and the ineffectiveness of medicinal and physical therapy, including roentgen ray, it

seemed logical to explore further the possibility of surgical help. Many approaches to the problem have been carried out by numerous surgeons, all aimed at interrupting the pain-conducting pathways coursing from the affected parts. Although none of these operations has been entirely successful, many of them have served as useful experiments. The injection of various sclerosing chemicals, alcohol in particular, paravertebrally and into the spinal subarachnoid space has been of no avail, and further consideration of this method of treatment does not seem profitable. There are three surgical procedures—anterolateral cordotomy, dorsal rhizotomy, and sympathetic ganglionectomy—that merit discussion, although their use singly or in combination has not

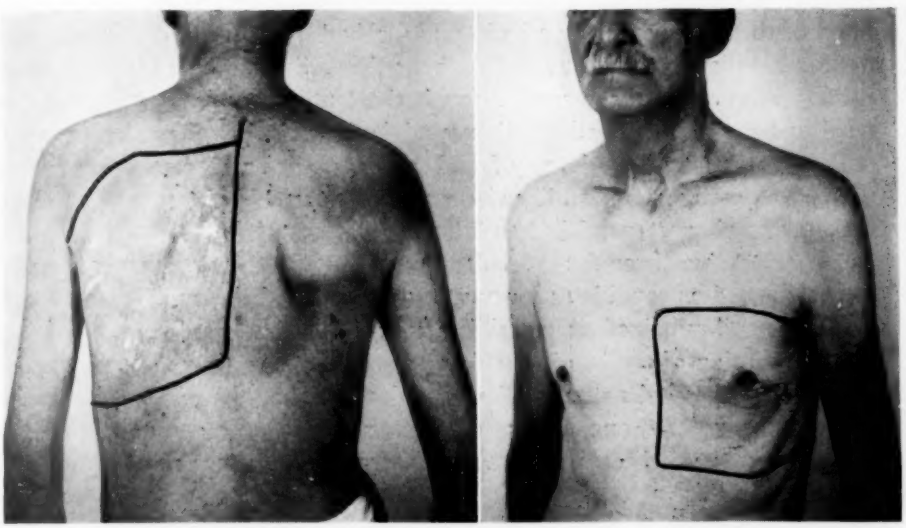

FIG. 4.—Patient with postherpetic neuralgia treated by anterolateral cordotomy and dorsal rhizotomy. The lines indicate the limits of the anesthetic and analgesic area. Relief of pain was not obtained.

resulted in complete relief of pain. The recitation of an abbreviated case report will suffice to review our experience with two of these three procedures.

A 67-year-old carpenter was admitted to the hospital complaining of burning and, at times, sharp shooting pain around the left thorax at the level of the T-7 and T-8 dermatomic zone. Two years prior to entry there had been a moderately severe attack of shingles, followed by pain described "as if someone was pulling on the skin of the chest with a pair of pliers." Many types of medicinal therapy had been tried, but so far as could be determined no opiates had been used. The left T-7 and T-8 dermatomic areas were mottled with irregularly bronzed skin and widely scattered whitish pocks. The first operation consisted of a right anterolateral cordotomy which effectually abolished appreciation of painful and thermal stimuli from the T-4 level distally on the left side. The loss of these modalities of sensation began at a point well above the upper aspect of the bronzed zone, yet the patient insisted that the pain was unaltered. Pressure over the segment of affected

skin with either a sharp or blunt pointed object precipitated a burning sensation, whereas before operation only the prick of the pin caused this type of pain. Because of the findings it was concluded that depriving the area of all form of cutaneous sensation might relieve him. Accordingly, a dorsal rhizotomy (T-3 through T-9) was performed. After this operation the zone of bronzed, implicated skin occupied about the middle of a completely anesthetic and analgesic area (Fig. 4). Pressure with any type of object along the bronzed zone still precipitated a burning type of pain. Moreover, spontaneous pain continued about as before the first operation. Six weeks following entry to the hospital the patient was discharged, complaining possibly more of the thoracic discomfort than when admitted. The neuralgia persisted until his death one year later in another hospital, death following an operation for prostatic hypertrophy with urinary retention.

Comment. Not all of our efforts have been so futile, for there are some patients who have had considerable relief following anterolateral cordotomy. Most of them, however, have had some residual discomfort; enough for them to question the worthwhileness of the procedure. Sympathetic ganglionectomy, namely removal of the second through the tenth thoracic ganglia, has been tried in two cases of postherpetic neuralgia of the lower thoracic region. In one, an anterolateral cordotomy failed to effect relief, and the ganglionectomy performed one month later likewise was ineffectual. In the second case sympathetic ganglionectomy failed to influence the neuralgia.

After passing through a period when patients with postherpetic neuralgia were excluded as candidates for any form of surgical therapy, it was decided that there still remained one possible approach that had not been given a trial, that is, excision of the involved skin and subcutaneous tissue. After explaining the experimental nature of the procedure to several patients who seemed appropriate subjects, one of them finally consented to the operation. The following summary indicates the clinical picture of the disease and the operative procedure in this case.

A 70-year-old man had had diabetes mellitus for eight years, and also had had attacks of angina pectoris at irregular intervals for four years. During the early part of January, 1945, there was first noted a band of pinkish-colored skin extending from the xiphoid region around the right side of the chest to the mid-line posteriorly. There was mild itching and some burning for the first six or seven days of illness. At the end of this time many small blebs began to appear, and within another two weeks the area comprising what was considered right T-7 and T-8 dermatomes was covered with varying-sized blebs. Medicinal measures, including injections of pituitary extract, were given in an attempt to relieve the constant burning pain, but were of little avail. Four roentgen ray treatments (300 r each) were given three days apart without appreciable amelioration of symptoms. By the end of seven weeks from the onset of the illness, the blebs had dried and the scales had exfoliated, leaving a band of bronzed pock-marked skin 7 to 8 cm. wide about the chest. In addition to the burning, boring type of pain, there were added periods of sharp shooting pain along the implicated dermatomic zone. Even opiates, which were eventually resorted to, failed to give sufficient respite for sleep. He was admitted to the hospital on June 5, 1945, at which time examination disclosed moderate arterial hypertension, mild cardiac enlargement, and diabetes mellitus. The findings of importance were related to the zone of irregularly bronzed skin somewhat mottled by the typical pocks of healed herpes zoster. The slightest touch of the skin caused the patient to withdraw quickly from the examiner's hand. It could be demonstrated that the shiny skin covering the larger pocks

was hypesthetic, but upon stimulating the involved area a burning pain was precipitated which continued for seconds after withdrawing the stimulus.

On June 6, 1945, under novocain anesthesia, a segment of skin 9 to 10 cm. wide and 60 cm. in length, including all of the bronzed area, was removed. Following complete healing of the wound the patient was discharged from the hospital on the twenty-first postoperative day (Fig. 5). All medication was discontinued and he remained comfortable until about the middle of April, 1946, when he noticed that touching a certain spot in the right anterior axillary line just caudad to the surgical scar produced a sharp shooting pain that radiated along the scar into the back. Examination at the time showed that either a pock had been overlooked at the operation or a new one had formed. Touching this single pock precipitated the pain. He was readmitted to the hospital on May 13, 1946, and a relatively small piece of skin including the offending pock was excised. Since the second

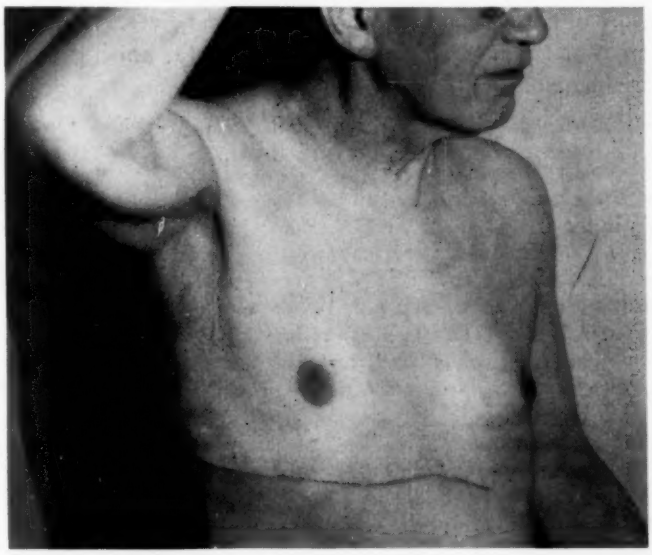

FIG. 5.—Patient for whom a zone of skin, 60 cm. in length and 9 to 10 cm. in width, was removed. Postherpetic neuralgia was completely relieved.

operation, he has remained comfortable as regards the postherpetic neuralgia, and when examined recently even rubbing the surgical scar produced no discomfort.

Comment. The result of this case demonstrated that fairly satisfactory relief of postherpetic neuralgia could be obtained by excision of the involved skin and the underlying subcutaneous tissue. Moreover, this experience seemed to indicate that the cutaneous nerve fibers and/or sensory receptors were a part of the abnormal neural mechanism responsible for the pain.

The second operation was carried out on a 60-year-old man. The bronzed and pock-marked skin was situated in the posterior part of the right T-7 dermatomic zone. One could demonstrate cutaneous hypersensitivity through the right half of the T-7 segment, but there was little if any discoloration of the skin anteriorly, and no pock marks were visible there. The drawing, burning pain, with occasional sharp stabs, was located in the area with obvious cutaneous changes. It was planned to perform the operation in two stages. The posterior half of the right T-7 zone, including the pock area,

was removed under local anesthesia. Generous undermining of skin permitted closure. Primary healing ensued.

Comment. The relief of pain was so complete that the patient refused to have the anterior segment of skin excised. When last seen three years after operation he had remained free of pain.

The third patient subjected to the operation, a man age 64, presented a clinical picture very similar to the first, and the treatment was the same except that the excision was performed in two stages. In this case, the burning pain was relieved but there has persisted an occasional sharp stab of pain "through the chest." The result, two years after operation, was considered moderately satisfactory.

Comment. Both the second and third patients were rugged, stoical individuals who had performed manual work all their lives. It seems possible that the third man had more pain that he would admit, sensing our hope that the result was satisfactory.

The experience with the fourth patient deserves more elaborate presentation than that accorded the second and third.

A 77-year-old man was admitted to the hospital on August 18, 1947, complaining of burning pain in the lower part of the back, upper hip, and around the lower abdomen on the right side. Occurring at irregular intervals, especially when these areas were touched, there was sharp stabbing pain of a radicular distribution. There had been an attack of shingles approximately one year before he entered the hospital, and according to to the story it had been rather severe and had lasted for three months. Examination disclosed the right T-10 and T-11 dermatomes to be mottled and extensively scarred, especially paravertebrally and over the right lower abdomen. On September 8, 1947, a segment of skin comprising the anterior half of the involved segment was excised. In order to close the defect, the skin was generously undermined down over the groin and regionally over the upper abdomen. Closure without undue tension was obtained, and this with the right lower extremity in full extension. Immediately postoperatively, the patient assumed a position of flexion of the right thigh to relieve the tension on the operative area. Considerable serosanguineous fluid accumulated in the free space created by the undermining procedure, although the area had been drained for 48 hours.

At the end of a week, the medial aspect of the wound opened, and discharge from this site continued for 3 weeks, leaving an indolent granulating area. After he was out of bed he walked in a stooped attitude and was not very co-operative in our attempts to have him "stretch" the skin of the right lower abdomen and groin. On November 27, 1947, the posterior half of the area of pock-marked skin was excised. The edges of this wound also partly separated, and the subsequent skin grafting to aid in epithelialization was not effective. Finally, after a rather prolonged period of treatment, the patient was discharged from the hospital. During the following year he was observed from time to time. There were so many complaints, many of which were not seemingly referable to the area under consideration, that it was difficult to evaluate them. Apparently the burning that was present prior to operation had disappeared. Roughing the affected part was said to produce pin and needle sensations. At irregular periods, there were recurring sharp stabbing pains in the region of the scar of the lower back and also in both lower extremities.

Comment. The difficulties, mostly the result of technical omissions in an elderly patient, have been recorded since it is obvious that many of them should have been avoided. The area deprived of skin and subcutaneous tissues should have been covered with a primary skin graft rather than closing the

wound after extensive regional undermining. In very elderly patients any discomfort is poorly tolerated; consequently if the situation producing the original complaint cannot be corrected without sequelae the advisability for any surgical therapy is questionable.

DISCUSSION

The mechanism for the production of postherpetic pain is not known. It has been reasonably well established that afferent impulses initiated by stimuli within a peripheral part do not traverse the ganglion cells of the dorsal root ganglia. This does not exclude the possibility that chronic pathological changes in a ganglion may in some manner lower the threshold of excitation in the cutaneous receptors. On the other hand, these obvious changes in a dorsal root ganglion as seen in examples of zoster may not be directly concerned in the production of postherpetic neuralgia, but merely represent the results of an active inflammatory process in this anatomical structure. It therefore seems proper to consider each anatomical component of the peripheral neural mechanism that may be involved in postherpetic neuralgia. A comparison of the findings in postherpetic neuralgia with those of other pathological states may somewhat elucidate the problem.

Skin lesions produced by accidental burns with various chemicals, when completely healed, may present an appearance very similar to the superficial residual of herpes zoster. Touch is not appreciated normally in the focally scarred areas, a finding somewhat comparable to that in zoster. The prick of a pin is also blunted in the scars in both conditions, but produces the spreading burning pain only in zoster. Moreover, the patients with scars from burns have not complained of the sharp stabbing pain so characteristic of postherpetic neuralgia. It therefore seems unlikely that the pathological process in the skin in zoster is the sole change that can be logically charged with the causation of postherpetic neuralgia.

The cutaneous sensory findings in zoster are almost identical with those characteristic of a "regenerating peripheral nerve." After division and suturing of a peripheral nerve in an anatomical position there follows, after variable periods, a return of appreciation of pin prick and differentiation of certain degrees of heat and cold. During this early phase of recovery touch is not appreciated and two-point discrimination is grossly altered. One may readily outline the denervated zone of skin by drawing a sharp object over the normal and onto the abnormal skin, as in zoster. Also, as in zoster, pin prick and excessive degrees of heat and cold when used as stimuli produce a spreading burning sensation, and roughing the part is also painful. In some patients there are, as well, sharp stabs of pain into the affected part, as described in postherpetic neuralgia. Therefore one cannot dismiss the possibility that the infection in some cases of zoster may produce a partial permanent interruption in peripheral nerves that may account for the neuralgia.

Primary lesions limited to the dorsal spinal roots are exceedingly rare. In two cases we have observed segmentally distributed cutaneous vesicles follow-

ing the spinal subarachnoid injection of alcohol. The promptness of the appearance of the blebs after injection made it appear that the effect of the alcohol on the spinal roots may have been responsible for their appearance. More likely, some of the alcohol penetrated the dorsal ganglion at the lateral extremity of the subarachnoid sleeve. The absence of vesicular eruptions following damage of dorsal roots by tumors as well as by surgical procedures of one sort or another makes it seem unlikely that a partial physiological interruption of these filaments by the inflammatory process incident to an acute attack of zoster could, at a later period, account for postherpetic pain. Finally, the segmental nature of postherpetic neuralgia would tend to exclude a lesion within the spinal cord as the causative factor.

Pain localized to a surface area, but due to a more central lesion, may be temporarily relieved by infiltrating the painful zone with an analgesic such as novocain. In some patients with this type of "reference pain," repeated infiltrations will eventually produce complete cessation of the discomfort. This therapeutic procedure is frequently used empirically in the treatment of pain of indeterminate origin, but has a sound pathophysiological basis. It has been used effectively during the acute phase in some cases of herpes zoster. Carrying the principle a step further, Dr. M. Frank Turney, the associate of one of us, two months ago undermined a large area of skin in a case of postherpetic neuralgia. In this patient the implicated skin was so situated that total excision did not seem feasible. Complete relief from pain followed the procedure. However, it is too soon after the operation to make an estimate regarding the ultimate outcome.

From our limited experience, total excision of the skin and subcutaneous tissue of the implicated dermatome offers a better chance of relief than any other method that we have employed. It would seem that the abnormal neural mechanism may be effectively altered by the excision of only a part of the involved dermatome, as was done in the second case of this series. On the other hand, in the first case, a single pock inadvertently left behind at the first operation was sufficient to preserve the abnormal mechanism. It is evident that total excision should not be carried out in some cases, particularly in patients with neuralgia of a part of the head or neck. It has been planned to denervate totally the area supplied by the first division of the fifth cranial nerve in ophthalmic neuralgia following zoster. A large flap of scalp and forehead could be outlined and reflected with the pedicle in the temporal region. Some weeks later, following the establishment of circulation, the pedicle could be sectioned. Various technical procedures may be devised to denervate the segment of skin involved, the best method probably being wide excision of the dermatome implicated.

SUMMARY AND CONCLUSIONS

1. Postherpetic neuralgia, an infrequent but distressing complication of herpes zoster, has been treated in the past by numerous medicinal and surgical measures, but usually to little avail.

2. After consideration of the resemblance of the sensory disturbances in this condition to those of other disorders characterized by a lowered threshold of the skin for various sensory stimuli, it was decided to excise experimentally all or portions of the implicated dermatome in a typical case of postherpetic neuralgia. The result achieved was so highly satisfactory that the procedure has been employed in other cases.

3. The four cases in which involved skin and subcutaneous tissue was excised have been reported in brief. The results were considered excellent in two, moderately satisfactory in the third, and unsatisfactory in the fourth case.

4. Pathological studies of skin excised at operation, as well as skin and other tissues obtained at autopsy from patients with herpes zoster but not subjected to "dermatomectomy," have been briefly recorded. The scarring and persistent inflammatory infiltration noted would appear to be competent contributing factors in the production of the pathological neural mechanism responsible for postherpetic neuralgia. The fact that not all victims of herpes zoster suffer from this complication poses a problem that remains obscure.

5. Proper evaluation of the reported surgical method of treatment for postherpetic neuralgia, and possible modifications of the procedure must await further trial.

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DISCUSSION.—DR. BRONSON S. RAY, New York, N. Y.: I can add very little to this discussion, but I should like to say that Dr. Browder's paper provides a much-needed fresh approach to an old and very troublesome problem.

In my experience, too, cordotomy and rhizotomy, and even lobotomy, while sometimes providing improvement, on the whole are disappointing in results. It is common and also somewhat paradoxical to find that local agents in the painful area, such as infiltration with procaine and spraying with ethyl chloride, will abolish the pain temporarily.

We have had one experience with the operation after it had been suggested by Dr. Browder. This was a woman 60 years of age, with chronic pain in a scarred band three or four inches in diameter running around the midchest on the right side. A two-stage excision necessitating a skin graft in part of the area was performed.

Whether due to incomplete excision, which is one definite source of failure, it seems to me, or the mental shortcomings of this particular patient, the result was only partially successful; but I am fully prepared to believe that the operation Dr. Browder proposes should provide success in carefully selected cases.

DR. FREDERICK E. KREDEL (Charleston, S. C.): So as not to make this thing seem too perfect, Dr. Browder asked me also to show a case of rather incomplete success. (Slide) This slide shows a person who had postherpetic neuralgia for six years. Blocks and intercostal nerve section did not relieve his extreme hypersensitivity. A wide

excision of skin was done from midline to midline on the right side well beyond the apparent area of hypersensitivity by testing. This gave him temporary relief, but a year and a half later there was full recurrence, and a second very wide excision was again done. Posteriorly, it was necessary to graft part of the area, as you see here.

An interesting fact is that these grafts, now a year and a half old, have shown no recovery of sensation, since they lie in a denervated field.

(Slide) On the anterior side it was not necessary to graft, but he still has some residual hypersensitivity and burning pain below the incision, and probably will require a third skin excision to complete the relief.

We have had two other cases that have had an incomplete result probably because not enough skin was removed.

DR. GILBERT HORRAX (Boston, Mass.): I just want to say that I think it is a very definite contribution which Dr. Browder has made to our conquest of pain; and just one word in elaboration of what Dr. Ray was saying about local infiltrations:

We have had three patients in whom local procaine injections over a fairly wide area, both in the trunk and one in the scalp, have given not temporary relief in the sense of a few days or a week or two, but relief that has lasted for six months or more. These people have come back at the end of that time for another injection. Some of them have come back many times.

In regard to these methods, I think Dr. Livingston could elaborate still further because he has had more experience with it than I have had. It is a very satisfactory method when it works.

DR. MIMS GAGE, New Orleans, La.: I will probably be out of order in what I have to say after congratulating the essayists on their excellent presentation, which will be of great help to us in treating intractible post-herpetic pain.

I would like to mention a method of treatment of the acute phase (which you probably won't believe) which will cure the disease and prevent undesirable sequelae. This consists in the intravenous administration of neoarsphenamine. One, two or three injections may be necessary. We usually give 0.3 Gm. and repeat this on the third or fourth day. This results in relief of pain and drying up of the lesions in 36 to 48 hours.

A friend of mine, Dr. Emile Block of New Orleans, has obtained relief of pain and cure in all 25 of his patients with herpes zoster treated by this method. He has used as much as 0.6 Gm. but usually gives 0.4 Gm. The results in his cases as well as in mine have been dramatic.

I suggest that you try this form of treatment in your next case. Of course, all the precautions necessary in the use of neoarsphenamine must be observed.

DR. JEFFERSON BROWDER (Brooklyn, N. Y.): I wish to thank the discussers. Of necessity this is a preliminary report.

In addition to the four patients who have been subjected to the operation mentioned here, there are six others I know of, three of them seemingly successfully operated on, one with a partial relief, and two failures. As stated, the operation is not considered a cure-all for post-herpetic neuralgia.

CLINICAL AND EXPERIMENTAL STUDIES OF FLUORESCEIN DYES WITH SPECIAL REFERENCE TO THEIR USE FOR THE DIAGNOSIS OF CENTRAL NERVOUS SYSTEM TUMORS*

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In the past, many investigators have recorded the use of dyestuffs to delineate malignant tissues with varying success. In most instances, it was found that the dye particles accumulated either in macrophage type cells of the tumor struma or in necrotic areas where the blood supply to the tumor had broken down. In no instance has an appreciable concentration of dye been demonstrated in intact viable tumor cells. This subject has been reviewed elsewhere.[5]

Sodium fluorescein has been injected into patients subjected to laparotomy with the hope that it might accentuate differences in the appearance of normal and malignant tissues. Approximately one gram of the dye (20 per cent aqueous solution) was injected intravenously four hours before the scheduled exploration of patients suspected of harboring an abdominal malignancy. If the injection rate was slow, no untold reaction occurred; rapid injection of the dye resulted in several cases of transient nausea and vomiting. It is well to warn the patient that his skin may be yellow for several days. Although staining of the skin usually disappeared in 24 hours, patients with liver insufficiency remained colored for longer periods of time.

Examination at time of operation was carried out under the ultraviolet light emitted by a CH-4 mercury vapor lamp equipped with a Wood's filter. In addition to the inspection of the tumors in situ, further study was made of sections of the removed specimens. A summary of these cases appears in Table I.

It was early noted that there was no specificity of the dye for tumor tissue but that inflammatory and cystic areas also fluoresced. The most consistent results were obtained with mucinous type carcinomas. In several instances lymph nodes involved by the carcinoma as well as the primary tumor exhibited a marked fluorescence. As noted elsewhere,[7] carcinomatous peritoneal implants usually fluoresced in contrast to the surrounding peritoneum. Although many interesting phenomena were encountered, the technic per se was not of any practical value.

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radioactive dye still present in the blood. In every case, the radioactive localization tests have been done without knowledge of the patient's history or physical findings. The results of these tests have been evaluated independently by members of the neurosurgical staff. The summary (Table III) includes only those patients in whom a lesion was later demonstrated to be present or proved to be absent by operation, ventriculogram, or angiogram.

It should be remembered that among those patients who were later proved to have a tumor, but in whom no tumor was localized by the radioactive dye technic, several had tumors too small (mainly cerebellar tumors), or of such a type (acoustic neuroma) as to contain less than the minimum amount of dye known to be necessary for detection. Other tumors that were not localized were usually found to be deeply situated. The easiest tumors to localize were those situated close to the cortex, malignant glial tumors, and those tumors accompanied by an appreciable amount of edema.

TABLE III.—*Localization of Intracranial Lesions with Radioactive Diiodofluorescein.*

Tumors correctly localized	22
No tumor localized, none demonstrated by angiogram, ventriculogram, or craniotomy	21
Correct localization (but vascular or demyelinization rather than tumor)	4
Close to, but not exact localization	3
Located as to hemisphere only	1
Tumor present but not located	20
Tumor localized but not found at operation, ventriculogram or angiogram	2
Incorrectly localized	2
Abscess not localized	1
Cholesteatoma not localized	1
Total	77

In order to study this technic more completely, tracer doses of radioactive diiodofluorescein were injected preoperatively, and biopsies taken of tumor and adjacent normal brain tissue at operation. Equal samples were then measured for their radioactivity. The activity found in human brain tumors ranged from 1.64 to 29 times that of adjacent normal brain.

In general, the highest ratios of activity were found in the more malignant tumors (glioblastoma). Some ratios were probably low because of difficulties in obtaining satisfactory "normal" brain tissue for comparison. For example, there is reason to believe that traumatized tissue or tissue momentarily deprived of its blood supply takes up an appreciable amount of dye. In other instances, a considerable time elapsed between obtaining the normal brain biopsy and the exposure of the tumor and the subsequent removal of a portion for measurement.

For further evaluation of the physical limitations of the radioactive dye technic, measurements were made of a human calvarium containing phantom tumors.[6] It was concluded that if the concentration of the dye in the brain tumor was twice that of the surrounding tissue, the minimal volume of a tumor that could be detected would be about 40 cc. If greater concentration ratios were present, smaller tumors could be detected.

To expedite the screening of various compounds for their usefulness as diagnostic agents, possible chemotherapeutic effects, and for radiation levels, brain tumors were induced in several strains of inbred mice. The technic employed utilized methylcholanthrene in a manner similar to that of Seligman and Shear[12] and Zimmerman and Arnold.[11] Since these tumors were induced in inbred mice, subsequent subcutaneous transplants could be carried out with facility. Several glial tumors have been carried for 17 transplant generations.

DISCUSSION

There is no complete explanation at the present time for the increased concentration of fluorescein dyes in brain tumors. That it is not due to a greater vascularity of the tumor is obvious from the fact that maximal fluorescence does not occur immediately after injection of the dye but gradually increases in intensity from one-half to four hours. It has also been demonstrated that tumors with the greatest blood supply (angiomas) are not very fluorescent, and, in fact, have resulted in two diagnostic errors.

Although the so-called blood-brain-barrier undoubtedly is partly responsible for the differential concentration of dye in brain tumors, that it is not wholly so is substantiated by the fact that some gastrointestinal tumors show a similar differential staining. Recent studies (unpublished) would seem to indicate that there is, perhaps, a specific affinity of tumor cells for the dye.

Since the experiments of Goldmann,[4] the theory of the blood-brain-barrier has occupied the attention of many investigators. Broman[2, 3] reported that the barrier exists in the intima of the blood vessels in the central nervous system. In experimental animals he was able to damage the barrier by injecting noxious substances into the carotid artery but not by applying them directly to the pia. He also found that the function of the blood-brain-barrier was impaired or absent in brain tumors, encephalomalacia, edema, abscesses, and multiple sclerosis. With this in mind, it is not surprising that we have found a slight fluorescence in areas of edema, and that the more edematous areas contain a greater amount of dye.

In this regard, it would seem that fluorescein and radioactive diiodofluorescein could be expected to be useful tools for further exploration of other diseases of the central nervous system, such as amyotrophic lateral sclerosis,[1] epilepsy, and other convulsive disorders. Fluorescein dyes are excellent for these purposes, since, (1) they are acid chromagen dyes and therefore should not penetrate the normal blood-brain-barrier, and (2) they can be detected and quantitated in extremely small amounts, either by fluoremetry, or by tagging them with radioactive isotopes.

The clinical use of other acid chromagen dyes such as Disulphine Blue* has been disappointing. Sufficient amounts of dye to produce sharp color differences between neoplastic and normal brain tissue, when viewed in ordinary light, also deeply stain the patient's skin. This circumstance has proved

* Imperial Chemical (Pharmaceuticals) Ltd., Manchester, England.

frightening to the patient, confusing to the anesthetist, and could result in serious medical-legal problems.

It is hoped that some of these compounds can be used clinically by tagging them with radioactive isotopes. By this method, very dilute solutions can be utilized.

SUMMARY

Sodium fluorescein has been shown to concentrate in an unpredictable manner in many tumors. The most consistent results were obtained in mucinous adenocarcinomas of the gastrointestinal tract and carcinomatous peritoneal implants.

In contrast, tumors of the central nervous system concentrate the dye in a consistent and predictable manner. The use of sodium fluorescein as an aid in the localization of brain tumors at operation is a simple and accurate technic which utilizes no special apparatus except a mercury vapor lamp.

Attempts to use radio-opaque dyes to outline brain tumors have not been successful. The clinical value of the radioactive dye method for the detection of brain tumors preoperatively cannot be evaluated completely at the present time. Better equipment, more sensitive Geiger-Mueller tubes, and other improved methods for detecting radiation should increase the accuracy and consistency of this method.

Mention has been made of the advantages of using fluorescein and radioactive dyes to explore further the role played by the blood-brain-barrier in other diseases of the central nervous system.

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THE CLINICAL USE OF RADIOACTIVE PHOSPHORUS IN THE SURGERY OF BRAIN TUMORS*

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IT HAS LONG BEEN RECOGNIZED that there is need for some physical or chemical method which will permit the accurate localization and demarcation of cerebral gliomas. Since the precise localization of subjacent cerebral tumors is often obscure even after exposure of the overlying cortex, and since an infiltrating glioma is frequently difficult to distinguish from adjacent normal brain, a number of efforts have been made to obtain such differentiation by the introduction of a substance into the circulating blood in the hope that it would preferentially localize in the tumor. Sorsby, Wright, and Elkeles[1] reported such attempts in 1942 employing a 10 per cent solution of kiton green. They were able to stain granulomatous tissue and traumatized brain but did not secure useful staining of gliomas. The same unsatisfactory results were obtained with Evans blue (T-1824) in small doses; this agent had the additional disadvantage in large doses of concentrating in subcutaneous connective tissue.[2] Moore and his collaborators[3] first succeeded in staining gliomas with a vital dye, fluorescein. They found that fluorescence of tumor tissue under ultraviolet illumination was obtained and that little or no fluorescence was demonstrated in adjacent normal tissue. Moore[4] was able also, by ingeniously tagging fluorescein with radioactive iodine, I^{131}, to obtain a method which was useful in the approximate localization of cerebral tumors externally through the skull.

This investigation has concerned itself with an attempt to discover a readily detectable substance which would demonstrate a higher concentration in cerebral tumor tissue, particularly in the gliomas, than in normal brain, in order that it might be employed for precise localization and demarcation of brain tumors at operation. It was decided to seek a radioactive material which, either because of a more rapid metabolic turnover in the lesion than in normal brain, or simply by virtue of a local breakdown in the blood-brain

* Dr. Selverstone was a Senior Fellow in Neurology, The National Research Council during a part of this study. The United States Atomic Energy Commission gave the radioactive phosphorus used in this investigation. The work reported here has been supported in part by an Institutional Grant of the American Cancer Society, the Office of Naval Research, and the National Foundation for Infantile Paralysis. This paper was read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

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barrier, would exhibit an increased concentration in cerebral tumor tissue. Certain theoretical considerations limited the search for this substance.

1. The most important requirement is that the substance must preferentially localize in the lesion to such a degree that an easily measurable difference in radioactivity can be demonstrated between the lesion and the surrounding brain.

2. It is necessary that the chemical toxicity of the substance be low in order to permit its use in adequate quantity.

3. The half-life of such a radioactive material must be sufficiently long to permit reasonable convenience in obtaining and storing it, and short enough to minimize the exposure of the patient to ionizing radiation.

4. In order to obtain precise localization it is important that the substance be a beta emitter with sufficiently soft radiation to be effectively absorbed within a relatively narrow area about the tumor. A gamma emitter such as Br^{82} Na^{24} or I^{131} would thus be unsuitable because of the extensive range of such radiation.

It was early suspected that the phosphate ion $HPO_4^{--} \rightleftarrows H_2PO_4^{-}$ might be a useful substance, since there was reason to believe that in all three of the major fractions ordinarily studied in tissue chemistry the phosphate ion might preferentially concentrate in tumor tissue when compared with normal brain. The importance of the phosphate ion as the major intracellular anion of the body would suggest a more rapid turnover of the substance in the *inorganic fraction* of a rapidly metabolizing tumor than in the relatively static normal brain tissue. The work of Changus, Chaikoff and Ruben[5] has demonstrated that the turnover of P^{32} in the *lipid fraction* of brain is low as compared with other organs. Since there was no reason to believe that this property would also be exhibited by gliomas, it was hoped that this fraction also might show an increased concentration of P^{32}. It was considered possible also that the high concentration of proliferating cell nuclei in tumor tissue as compared with normal brain might be reflected in an increased uptake of P^{32} in the nucleoproteins of the *protein fraction*.

In addition to these metabolic considerations, the phosphate ion was considered a likely material in view of the work of Friedemann[6] who has shown that the effectiveness of the blood-brain barrier is greater in the case of negatively charged than of other particles. If a local defect of the barrier exists in the tumor, we might thus be provided with a mechanism for differential uptake.

The extensive employment of P^{32} in large therapeutic doses in polycythemia vera and in certain of the chronic leukemias[7] without dangerous toxicity suggested that it could be used with relative safety in this study.

The half-life of P^{32} 14.3 days, is a convenient one and its emission consists of pure negative beta radiation with a maximum energy of 1.69 Mev. This energy level has been shown to permit a maximum penetration in brain tissue (assuming a density of 1.0) of approximately 7 mm.[8]

A preliminary study[9] demonstrated to our satisfaction that in glioblastoma multiforme and in astrocytoma, as well as in certain nongliomatous intracranial tumors, a very satisfactory difference in the uptake of radioactive phosphorus, P^{32} was present when tumor was compared with normal brain. The patients of this early group were studied employing doses of from .8 to 3.8 millicuries of radioactive phosphorus, P^{32} as buffered phosphate ion. The specimens of tumor and of normal brain were obtained at operation or at autopsy. An "activity ratio," representing for equal weights $\frac{\text{radioactivity of tumor}}{\text{radioactivity of white matter}}$ was found to vary from 5.3 to 110. This ratio appeared to be eminently satisfactory for purposes of localization, and accordingly studies were next directed toward the development of a suitable miniature Geiger-Mueller counter which could be employed as a probe for the accurate localization and demarcation of these tumors.

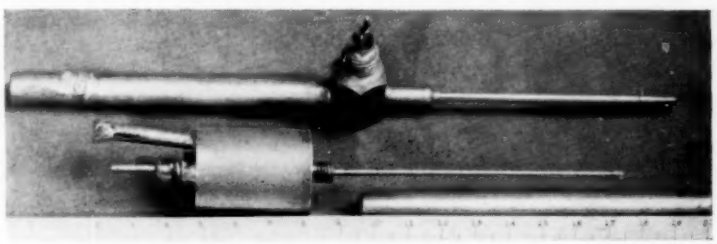

FIG. 1.—The 3 mm. and 2 mm. probe Geiger-Mueller counters, employed in localization and demarcation of cerebral tumors.

In order that a Geiger-Mueller counter might be used as a probe within the brain, it was considered desirable that the dimensions of the portion entering the brain approximate those of the ventricular needles customarily employed for this purpose. Since it is important that the depth of the neoplasm as well as its surface projection be determined, it was considered necessary that the sensitive volume of the counter be located near the tip. When this research was undertaken, no such counter was available. It was essential to find a suitable combination of noble and quench gases and to determine optimum pressures for counters of these dimensions, as well as to develop a technic of construction. The first counters used at operation were 5 mm. and 3 mm. in diameter and were filled with an argon-ether mixture.[10] For several months 3 mm. counters filled with argon-ethyl acetate have given good service. More recently, 2 mm. counters of this type have been used. The probing portion of such a counter is, therefore, of diameter comparable to that of a ventricular needle.

The counters are sterilized by immersion in a formalin germicide for 20 minutes or more. The cable connecting the counter to the associated apparatus is autoclaved. The preamplifier and scaling circuit remain outside the sterile field.

In a brief preliminary report[11] our use of the earlier argon-ether counters in the location of 14 deep brain tumors was noted. This work has been amplified, and it is now possible to report 33 cases in which the method has been employed chiefly for localization, but also for demarcation of tumors from surrounding brain.

METHOD

The patient is given a single intravenous injection of buffered radioactive phosphate ion of from .95 to 4.2 millicuries preferably at least 24 hours before operation, but time intervals of from 1.8 to 186.8 hours have been employed.

TABLE I.—*Localization of 14 Glioblastomas by Means of the Probe Counter, with Attempt at Demarcation for Total Extirpation in Six Cases*

Case	Time in Hours After Injection of P^{32}	Corrected Counts per Minute		Ratio of Counts	Useful for Demarcation of Tumor
		Tumor	Brain		
H.F.	3.3	2238	99	22.6	−
E.P.	13.4	684	55	12.4	−
G.H.	17.0	1982	27	73.4	−
A.G.	19.3	12668	2168	5.8	+
J.D.	21.0	2128	222	9.6	−
F.F.	21.1	2125	219	9.7	+
A.H.	22.7	1134	35	32.4	+
A.P.	25.3	30077	828	36.3	+
A.C.	25.6	2946	482	6.1	−
W.B.	26.8	8829	349	25.3	−
A.A.	26.9	4539	783	5.8	+
A.B.	43.6	13032	1207	10.8	−
D.C.	46.5	2885	390	7.4	+
M.G.	186.8	2034	250	8.1	−

No other preparation of the patient is necessary. The appropriate standard methods of approximate brain tumor localization are fully utilized, and the location of the exposure to be made of cerebral or cerebellar cortex is determined by neurologic examination and by electroencephalographic and ventriculographic data.

A "control area" is first chosen, usually in the periphery of the exposed field, in the region considered least likely to be the site of tumor. The sensitive volume of the counter is introduced into the brain and counts recorded for a statistically significant time interval, usually 0.4 minute, at various depths beneath the surface. We now ordinarily count first at 1 cm. and then at successive increments of 1 cm. to a depth of 4 to 6 cm., as required. The counter is then employed in suspected regions in a similar manner until a sharp increase in counting rate indicates that neoplasm has been struck. After the tumor has been located in this manner, the counter is cleansed with hydrogen peroxide in order to prevent possible spread of malignant cells, and successive approaches are made from normal brain toward tumor in an attempt to demarcate its boundaries. In those instances where radical removal by lobectomy or bloc dissection can be carried out without sacrifice of the

motor cortex or sensory speech area, resection is accomplished, taking a margin of 1 to 2 cm. or more from sites where abnormal counts have been obtained.

Tables I and II show counting rates obtained with the probe counter in 28 cerebral tumors of various types as contrasted with normal brain in the

TABLE II.—*Localization of 14 Other Cerebral Tumors by Means of the Probe Counter, with Attempt at Demarcation for Total Extirpation in Six Cases*

Case	Time in Hours After Injection of P^{32}	Corrected Counts per Minute		Ratio of Counts	Histologic Type	Useful for Demarcation of Tumor
		Tumor	Brain			
W.F.	18.7	812	114	7.1	Astrocytoma	+
D.W.	26.2	4182	514	8.1	Astrocytoma	+
H.H.	65.8	2056	270	7.6	Astrocytoma	+
A.T.	93.8	777	112	6.9	Astrocytoma	+
W.P.	15.3	1673	82	20.4	Medulloblastoma	−
A.H.(2)	61.7	24232	2852	8.5	Astroblastoma	−
B.B.	16.4	7843	137	57.1	Oligodendroglioma	+
W.B.(2)	42.2	627	105	6.0	Ependymoma	−
D.M.	5.7	1650	100	16.5	Unclassified glioma	−
A.S.	19.7	1337	67	20.0	Unclassified glioma	+
J.S.	1.8	5226	961	5.4	Unclassified glioma	−
M.M.	43.5	4523	159	28.4	Angiosarcoma	−
W.H.	16.5	2136	64	33.3	Metastatic carcinoma	−
G.J.	19.5	755	26	29.0	Metastatic carcinoma	−

same patient. In five instances, tumor presented on the surface and location by means of the counter was not necessary. In 12 cases data obtained in counting was employed in an attempt to demarcate the tumor in order to facilitate its radical removal.

Figures 2 and 3 illustrate the technic of left (major) temporal lobectomy in case C.B. (not in Table I), using the probe counter in order to demarcate

TABLE III.—*Case C. B.: Demarcation of Glioblastoma with Left Temporal Lobectomy, 24.1 Hrs. after Injection of P^{32}*

Depth	Counts per Minute	
	3 cm.	4.7 cm.
B	77	117
A	431	564
C	520	932
E	109	512
D	105	124

the tumor. Point B is in the "control area." Abnormal counts were obtained at depths of both 3 cm. and 4.7 cm. at points A and C (Table III), while a deep tongue of tumor tissue was demonstrated only at 4.7 cm. at point E. Counts were again normal at point D. Resection was carried out through what appeared to be normal tissue, the plane of the incision passing just below

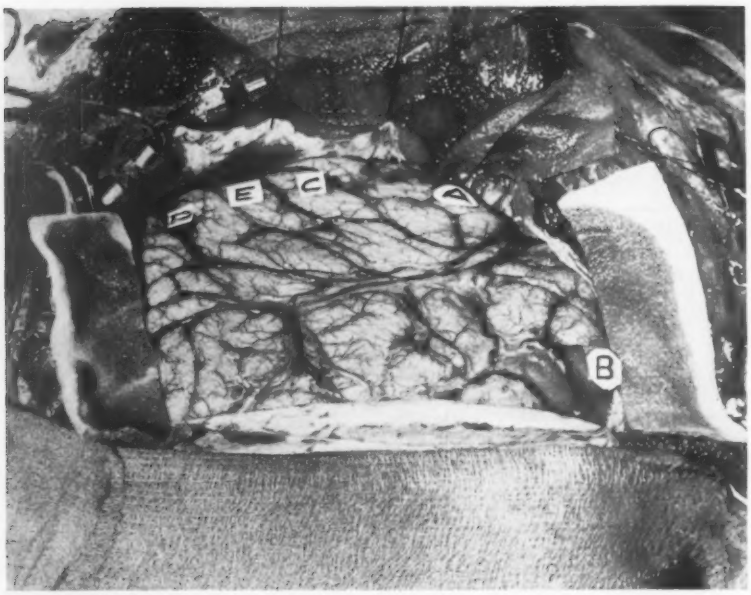

FIG. 2.—Case C. B. See Table III. Demarcation of glioblastoma prior to left temporal lobectomy.

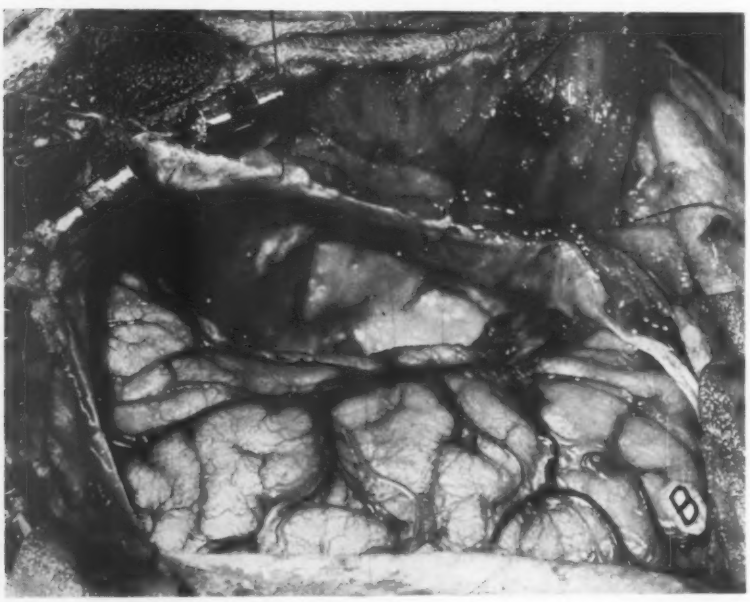

FIG. 3.—Case C. B. Appearance of the brain following left temporal lobectomy.

the Sylvian vessels and through point D posteriorly. Speech was only temporarily impaired following the procedure, although his subsequent course nine months after operation would suggest that the tumor, a glioblastoma multiforme, was not completely extirpated.

Table IV shows four cases in which a tumor was not localized by means of the counter. We may expect, as in case R. H., where virtually the entire cerebral hemisphere was infiltrated by gliomatous cells, to find this method of no value, since no normal area is available for comparison. An occasional small, deep tumor may also be missed, as in cases I. C. and C. E., since the method is effective only when the counter approaches within approximately 5 mm. of the tumor. Case G. T., in whom no tumor was found, is being followed, but it now appears likely that this patient does not have a cerebral tumor.

TABLE IV.—*Four Cases in Which No Tumor Was Identified by Means of the Probe Counter*

Case	Subsequent Findings	Classification
R.H.	Diffuse gliomatosis. No normal area was available for control.	Clinical limitation of method.
I.C.	Counter was introduced to 5.0 cm. Tumor in uncus and peduncle began at 6.5 cm. in P. M. specimen. P. M. ratio 5.8:1.	Error in application of method.
C.E.	Deep metastatic nodule 1.2 cm. in diameter. Counter missed tumor by 0.5 cm.	Error in application of method.
G.T.	Patient made complete clinical recovery and has remained well for 9 months	No tumor. Method presumably correct.

SUMMARY

Radioactive phosphorus, administered intravenously, has been used clinically in order to localize and demarcate brain tumors. Its high concentration in cerebral tumors as compared with normal brain was suspected on theoretical grounds, and now appears to be adequately confirmed. A Geiger-Mueller counter of diameter comparable to that of a ventricular needle has been employed at operation in 33 cases in an attempt to localize intracranial tumors. Data adequate for localization was obtained in 29 cases, in 23 of which the tumor did not present on the surface. In one case, diffuse gliomatosis, the method was intrinsically of no value, and in two cases the method was not adequately employed. In one instance no tumor was located, and the clinical course would suggest that none is present.

In 13 cases an attempt has been made to demarcate the tumor for bloc resection or lobectomy through normal tissue. A later communication will report results and limitations of this method when applied to the radical surgery of the gliomas.

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Discussion.—Dr. Francis C. Grant, Philadelphia, Pa.: We have attempted to identify intracranial tumors specifically with dye, using Nile blue instead of the fluorescein salt. We have not as yet had sufficient experience to speak with any certainty, but in four cases, the tumor was stained definitely and specifically blue, in contradistinction to the surrounding brain. Something of this kind, it seems to me, will be of extreme importance in the neurosurgery of the future, because certainly the limitations of these tumors, particularly the infiltrating gliomas, are difficult to determine by the naked eye alone, and unless complete extirpation is possible, a recurrence will, of course, take place.

At the present time I am not certain of the importance of these drugs prior to the opening of the skull. Even if radioactive material can be attached to the dye which impregnates the tumor specifically and then the area of increased radiated material picked up with a Geiger counter, the value of this method of localization may not be much of an improvement over the use of air. However, when once the skull has been opened and the brain exposed, to be able to outline the size of the tumor accurately by contrast staining methods, so that the surgeon can be certain that complete extirpation has been accomplished, is a matter of great importance. The only way that a brain tumor can be cured is by total and complete extirpation.

There is another possibility inherent in the use of these dyes. It was stated that the amount of material taken up by the tumor depended upon the cellularity of the growth. If, by the use of these dyes, it would be possible to make a differential diagnosis preoperatively between the very cellular and the relatively acellular types of glioma, this would be important. Anything that will lead us to believe that we are dealing with a glioblastoma multiforme prior to operative procedure would save the patient and the neurosurgeon an unnecessary operative procedure. If it is possible to make this differential diagnosis with certainty by this method, it will be a long step in advance.

DR. WILDER PENFIELD (Montreal, Canada): The fluorescein method and the use of radioactive phosphorus are studies of great importance. They should be pushed. Neither method has come to a point where it can be generally adopted. The same can be said for the use of the electrocorticogram with the electrodes placed on the cortex. This latter method might locate a neoplasm but biopsy is still needed.

Actually, the application of the two methods described today is only to the infiltrating tumors, not to the benign ones which we can get out and which we can localize by other means, ventriculography particularly. It is still necessary to fall back upon exposure and inspection of the brain.

I have always been very much interested in pathological study, and we always do biopsies of infiltrating brain tumors before removal. Gross inspection is usually sufficient to indicate the situation of neoplasm but biopsy must be relied upon for prognosis.

DR. GEORGE E. MOORE (Minneapolis, Minn.): I do think that sodium fluorescein can be used to good advantage clinically. Dr. W. T. Peyton and Dr. Lyle French of our clinic have found it helpful especially in the localization of tumors whose position has not been completely elucidated by ventriculography.

As to radioactive diiodofluorescein, I think it is more important as a research tool than as a diagnostic measure at the present time. This technic should be quite valuable in the future for the study of other diseases of the central nervous system as those studied by Dr. Robert B. Aird (*i.e.* amyotrophic lateral sclerosis) and others which are intimately associated with damage to the so-called blood-brain-barrier. Among these diseases might be certain forms of epilepsy. In the latter instance, sodium fluorescein may be of some value for the localization of epileptogenic loci that cannot be determined readily by ordinary visual means.

DR. B. SELVERSTONE (Boston, Mass.): I should like to thank Dr. Grant and Dr. Penfield for their discussion. May I say, however, that in our hands, since we have had a lot of experience with the technic, we have found this to be a practical clinical tool of great value. I should like to tell of one case which may point this out:

One month ago a patient was admitted to the private service with signs and symptoms of a cerebellar tumor apparently in the right hemisphere. After ventriculography and other studies, which confirmed the presence of a cerebellar tumor, operation was carried out. The cerebellum was explored and was found to be entirely normal in appearance. The aqueduct was patent. The wound was closed.

The patient proceeded to do very poorly. He developed papilledema which had not previously been present, and his flap bulged considerably. One week ago he was given two millicuries of radioactive phosphorus. On the following day he was taken to the operating room, his flap was reopened, the cerebellum exposed, and again it appeared to be entirely normal.

(Slide) This slide shows the findings with the Geiger counter. It was introduced first into the left lobe of the cerebellum, and you can see the counts at 1, 2, 3, 4 and 5 cms. It was then introduced into three places in the right cerebellum hemisphere, and again you can see the counts. Notice that these counts are all rather low—from 14 to 176 counts per minute. No tumor was found.

The counter was next introduced into the vermis: At 1 cm. there were 304 counts per minute. At 2 cms. there were 1080 counts, and so on up to 4 cms., where 1560 and 2136 counts were obtained in two loci. In the vermis at a depth of a little over 1 cm. a large glioma was encountered, and a subtotal removal was undertaken. Since that time the patient has done reasonably well.

EVALUATION OF TOTAL SYMPATHECTOMY*

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IN THE EVOLUTION OF OPERATIONS on the sympathetic nervous system for the treatment of hypertensive vascular disease, a dictum frequently proposed has been that the degree of success is proportional to the extent of the sympathectomy. This assertion has some times been tempered by adding that the purpose of the operation should be the denervation of as large an area of the body as is necessary yet reasonably safe. The earlier types of limited operation came to be largely supplanted by the thoracolumbar resection from the eighth or ninth thoracic to the upper lumbar levels proposed by Smithwick[1] ten years ago. Peet[2] changed to a higher resection of the thoracic sympathetics in his supradiaphragmatic operation. More recently others (Poppen,[3] and Hinton and Lord[4]) have extended the resection of the thoracic chain up to the third or fourth thoracic ganglia, and have implied that blood pressure lowering effects were better. A logical conclusion would seem to be that consistently good results might be expected if total sympathectomy were performed, providing, of course, the patient could tolerate the operation and not be left a "homeostatic cripple." Grimson[5] reported before this Society eight years ago his performance of total paravertebral sympathectomy in three patients and he has presumably added to this number since.

Since neither the etiology of hypertension nor the mechanism by which sympathectomy exerts its beneficial effects are known, proof for the superiority of one type of operation over another should rest on the comparison of results. However, the unpredictable nature of hypertension makes the evaluation of any form of treatment difficult, and it is even more troublesome to try to measure the relative merits of different types of operation. In this report, which deals with the results of total paravertebral sympathectomy in 30 hypertensive patients, some comparative statistics have been included for whatever value they may have. Also, an attempt has been made to estimate the effects of successively more extensive sympathectomy in the same patient. Some of the mechanisms responsible for the beneficial effects of total paravertebral sympathectomy, and some of the reasons for its failure to accomplish all that might have been expected, are reviewed in the light of these data.

Material.—The patients in this series of 30 were each selected for total paravertebral sympathectomy because it was felt that some complicating factor or factors in their hypertensive disease would be more likely to respond to a wider sympathectomy than has usually been employed in this clinic (Ray[6]). It should be evident that the majority were poorer operative risks

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than obtains in the general average of hypertensive patients subjected to sympathectomy. Patients with angina pectoris (17) and patients with retinal hemorrhages or papilledema (Groups III and IV retinopathy, according to the classification of Keith, Wagener & Barker[7]) constitute the bulk of the series; some of these also had vasospastic states of the extremities or palpitation and tachycardia. The remainder had only vasospastic disorders, tachycardia and palpitation as initial symptoms in their disease, or following the thoracolumbar type of operation.

Of the six patients who had thoracolumbar (T8-L3) sympathectomies previously, one had little improvement in blood pressure and angina and later developed retinal hemorrhages. Two had a persistence of their severe angina pectoris and a return of blood pressure to preoperative levels. One had a persistence of mild angina, and developed tachycardia, palpitation and Raynaud's phenomenon of the upper extremities. One had Raynaud's phenomenon in the hands, tachycardia and palpitation, but a good lowering of blood pressure in response to thoracolumbar sympathectomy.

Of the 24 patients in whom total sympathectomy was done as a primary procedure, nine had Group III retinopathy and 11 had Group IV; ten of these patients also had angina pectoris. The remaining six patients had Group II retinopathy, of which three had angina pectoris, one had scleroderma and one, a 53-year-old man, had a fixed diastolic pressure of 150 mm. of mercury.

The pertinent data regarding these patients are tabulated in Table I and summarized in Table II.

Method of Operation.—The operation of total bilateral paravertebral sympathectomy from stellate to the third lumbar ganglia was carried out in two, three and four stages in this series. For the 24 patients in whom the total operation was planned initially, a two-stage operation (one side at a time with an interval between varying from two to four weeks) was performed in eight patients. In 16 the operation was carried out in three stages, employing a total sympathectomy on one side first, next a thoracolumbar (T7 or 8 to L3) on the other side in about two weeks, and finally a completion of the thoracic sympathectomy on the second side, usually in two weeks. But in six patients it was found desirable to delay the final stage for three to 16 months.

For six patients who had previously had thoracolumbar (T7 or 8 to L3 and splanchnic nerve) sympathectomy the remainder of the thoracic sympathetics, including the stellate ganglia, were removed in one bilateral operation in three patients and in two operations in the other three. The time interval between the thoracolumbar operation and completion of the total sympathectomy was 12 to 30 months. Together with their original operations these patients had a total of two, three or four separate operations.

The anesthesia employed in all operations was endotracheal ether and oxygen preceded by intravenous pentothal induction. The operative approach to the sympathetics was retroperitoneal and retropleural. The thoracolumbar

part of the operation employed resection of the proximal ends of the eleventh and twelfth ribs, detachment of the diaphragm, and incision in the lumbar fascia. Through this exposure the lumbar chain was resected to a point below the contribution of the third lumbar rami, and the thoracic chain together with the great splanchnic nerve was freed to a point above the contribution of the seventh or eighth thoracic rami. The thoracic sympathetics were divided here unless the operation was to be completed at once, in which case they were tucked into the upper part of the exposed paravertebral gutter and the

TABLE I.—*Preoperative Data, Type of Operation, Postoperative Data and Period of Observation After Total Sympathectomy in 30 Patients. Changes are Graded Slight (sl), Moderate (mod), and Marked (mk). T-L-Thoracolumbar Sympathectomy.*

			PREOPERATIVE DATA								
Patient No.	Sex	Age	Diastolic Blood Pressure	Eye Ground Group	Angina Pectoris	Enlargement of Heart	E.K.G. Changes	Cardiac Failure	Renal Impairment	Cerebral Involvement	Degree of Disability
1	M	32	170	IV	0	0	Mod.	0	Mod.	0	Mk.
2	M	34	160	IV	+	Sl.	Mod.	Mod.	Sl.	0	Mk.
3	F	29	170	IV	+	Sl.	Sl.	Sl.	0	Sl.	Mk.
4	F	31	160	IV	+	Sl.	Mod.	Mod.	Mod.	0	Mk.
5	M	48	170	IV	0	Sl.	Sl.	0	0	0	Mk.
6	M	40	140	IV	0	Sl.	Sl.	0	0	0	Mk.
7	M	43	160	IV	0	Sl.	Sl.	0	Sl.	0	Mod.
8	F	31	120	IV	0	0	0	0	Mod.	Mod.	Mk.
9	M	43	170	IV	0	Sl.	Sl.	0	Sl.	0	Mk.
10	F	38	124	IV	0	Mod.	Sl.	Mod.	0	0	Mk.
11	F	49	140	III	0	Sl.	Sl.	0	0	Mod.	Mod.
12	F	47	130	III	+	Sl.	Sl.	0	0	0	Mod.
13	F	40	120	III	+	Sl.	Sl.	Sl.	0	0	Sl.
14	F	40	130	III	+	Mod.	Mod.	Sl.	0	0	Sl.
15	M	48	150	III	0	0	Sl.	Sl.	0	0	Mod.
16	M	48	140	III	0	Mod.	Sl.	0	0	0	Sl.
17	F	45	140	III	+	Sl.	Sl.	0	0	0	Mod.
18	F	50	170	III	+	Mk.	Mk.	Mod.	Sl.	0	Mk.
19	M	53	150	II	0	Mod.	Mod.	Sl.	Sl.	0	Mod.
20	M	45	120	II	+	0	Sl.	0	0	0	Mod.
21	M	43	110	II	+	Sl.	Sl.	0	0	0	Sl.
22	F	37	160	III	+	Sl.	Sl.	0	0	0	Mod.
23	F	32	150	II	+	Mod.	Mod.	0	0	0	Mod.
24	F	45	120	II	+	Mod.	Mod.	Sl.	0	0	Mod.
25	M	42	110	II	+	Sl.	Mod.	0	0	0	Mod.
26	F	28	90	II	0	0	Sl.	0	0	0	Sl.
27	F	44	120	II	0	Sl.	Sl.	0	0	0	Sl.
28	F	51	160	IV	+	Mod.	Mod.	Sl.	0	Mod.	Mk.
29	M	52	150	III	+	Sl.	Sl.	Sl.	0	0	Sl.
30	F	49	160	II	+	Mod.	Mod.	Sl.	0	0	Sl.

wound closed. A second incision for removal of the remainder of the thoracic sympathetics was made parallel to the spine to permit resection of the proximal several centimeters of the third, fifth and sixth ribs. After reflection of the pleura through this exposure the ganglionated chain was freed from the stellate to the sixth or seventh thoracic ganglia, as the case required. In the one-stage operation the entire ganglionated chain from stellate to L_3 ganglia, with the attached splanchnics (and sometimes the celiac ganglion), could be lifted out intact. The celiac ganglia were removed on both sides in eight patients and on one side in two.

Patients were placed on the operating table in the lateral position, slightly tilted forward for both the upper and lower incisions, except for two patients placed in prone position on the "cerebellar" table for the performance of bilateral upper thoracic sympathectomy. The average time required for the performance of a one-stage total sympathectomy on one side was two hours. During the operation patients received intravenous 5 per cent glucose in water, sometimes supplemented by blood transfusion and neosynephrine, one or both.

TABLE I.—(*Continued*)

POSTOPERATIVE DATA

Patient No.	Operations	Diastolic Blood Pressure	Fall in Diastolic Blood Pressure	Eye Ground Groups	Degree of Rehabilitation	Follow-up Period
1	2 stage total with celiac gangl.	120	50	II	Mk.	2 years
2	3 stage total.	140	20	II	Mk.	2 years
3	2 stage total.	120	50	II	Mk.	2 years
4	2 stage total with celiac gangl	150	10	II	Mk.	2 years
5	2 stage total.	114	56	II	Mk.	2 years
6	3 stage total.	100	40	II	Mk.	2 years
7	3 stage total with celiac gangl.	90	70	II	Sl.	2 years
8	3 stage total.	120	0	II	Mk.	2 years
9	2 stage total with celiac gangl.	130	40	II	Mk.	1½ years
10	3 stage total.	100	24	II	Mod.	1½ years
11	3 stage total with celiac gangl.	120	20	II	Mod.	2 years
12	3 stage total.	110	20	II	Mk.	2 years
13	2 stage total.	90	30	II	Mk.	2 years
14	3 stage total.	110	20	II	Mk.	2 years
15	3 stage total.	120	30	II	Mod.	1½ years
16	3 stage total with celiac gangl.	100	40	II	Mk.	1½ years
17	3 stage total.	88	52	II	Mod.	1½ years
18	3 stage total.	110	60	II	Mod.	1 year
19	3 stage total.	100	50	II	Mk.	2½ years
20	3 stage total.	90	30	II	Mod.	1 year
21	2 stage total. . . . . Prev. T-L	90	20	II	Sl.	1 year
22	27 mos.—1 stage upper thoracic. . .	160	0	II	Mk.	2½ years
23	12 mos.—1 stage upper thoracic. . .	130	20	II	Mk.	2½ years
24	26 mos.—2 stage upper thoracic. . .	100	20	II	Mod.	2 years
25	12 mos.—2 stage upper thoracic. . .	120	0	II	Mk.	2 years
26	20 mos.—1 stage upper thoracic. . .	70	20	II	Mod.	2 years
27	30 mos.—2 stage upper thoracic. . .	80	40	II	Mod.	2 years
28	3 stage total	Died after 11 months				
29	2 stage total	Operative death				
30	3 stage total	Operative death				

Mortality.—Among the 30 patients, two deaths occurred as a result of operation (6.3 per cent). One of the patients (No. 30) had a high grade of hypertension and angina pectoris, and died on the operating table at the end of a third-stage operation, presumably of heart failure. The other patient (No. 29) had angina pectoris and advanced retinopathy; he died of a painless coronary infarction 24 hours after completion of the second stage of a two-stage operation.

One other patient (No. 28) died suddenly at home 11 months after operation, presumably of cardiac failure due to coronary disease. She had been relieved of angina pectoris and otherwise improved after operation.

Postoperative Complications.—Pleural effusion was the most frequent complication after operation, due, it is believed, to the extensive manipulation of the pleura and to the high incidence in this series of borderline cardiac decompensation. It occurred in nine patients, and in four, one or more aspirations of the effusion were required. In most of the patients digitalization and the administration of mercurial diuretics were of value.

Cardiac failure occurred after unilateral total sympathectomy in three patients with borderline cardiac compensation but there was quick improvement following the use of digitalis, oxygen therapy and mercurial diuretics.

TABLE II.—*Grouping of 30 Cases of Total Sympathectomy According to Grade of Hypertension and Accompanying Symptoms*

		No. of Cases
Advanced grade of hypertension		21
With Group III retinopathy	10 cases	
With Group IV retinopathy	11 cases	
Of these 11 had angina pectoris.		
Angina pectoris and less advanced hypertension (Group II retinopathy)		6
Less advanced hypertension		3
With Raynaud's phenomenon and tachycardia	2 cases	
With cler derma	1 case	
Total		30

In six of the 30 cases there were intervals of one to two and one-half years between thoracolumbar and total sympathectomy. Conditions leading to additional operation were:

Angina pectoris	3 cases
Angina pectoris and retinal hemorrhages	1 case
Raynaud's phenomenon	2 cases

As a result of this experience early in the series, digitalis was used preoperatively more commonly thereafter when there was any question of the state of the cardiac reserve.

One patient (No. 3), a 29-year-old woman with advanced hypertension, became comatose shortly after reacting from anesthesia following the second stage of a two-stage sympathectomy. The temperature rose to 41°, there were shifting neurologic signs, and consciousness was not regained for eight days; the spinal fluid during this period was normal. She eventually made a good recovery. The complication is thought to have resulted from anoxia to the brain during the operation and thereafter, during a period of low blood pressure.

The course of convalescence and degree of rehabilitation after operation varied widely but on the whole the variations were not significantly different after the lesser operation of thoracolumbar sympathectomy. The measure of rehabilitation is indicated in Table I.

THE EFFECTS OF THE OPERATIONS ON THE HYPERTENSIVE STATE

Excluding two patients who died in the hospital and one who died before the end of a year, 27 were repeatedly examined from one to two years after operation, and the latest postoperative observations are the ones recorded in the comparative pre- and postoperative evaluation. Table I provides much of the data in tabular form.

Effects on Blood Pressure.—The effect of the operation on blood pressure is interpreted by comparing the average preoperative reclining diastolic pressure with the highest postoperative diastolic pressure. In the surviving 21 patients who had initial total sympathectomy there are nine (43 per cent) who now have diastolic pressures consistently of 100 or less mm. of mercury; the remaining 12 all had some lowering of their diastolic pressure, and at least six may be said to have had a significant lowering to a much safer level

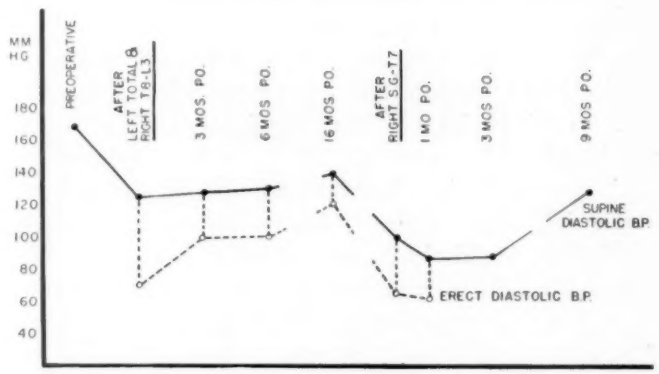

FIG. 1.—Patient No. 18. Effect on diastolic blood pressure of total sympathectomy after the first two stages (lt. stellate to L3 and rt. T8 to L3) and after delayed third stage (rt. stellate, S.G., to T7).

than originally existed. This record is perhaps better than might be expected from the thoracolumbar operation, but the number of this series is small and the types of cases make comparison unreliable.

In six of the 21 patients who had "initial" total sympathectomy there was a lapse of from three to 16 months between the second and third stages of the operation, that is, before the final resection of the remaining portion of the upper thoracic chain on one side. Figure 1 shows the effect on diastolic blood pressure and postural hypotension after a delayed third stage of a total sympathectomy in patient No. 18. In all of these patients there was an additional fall in diastolic pressure of 20 mm. of mercury, or more and an increase in postural hypotension. In three the effect was transient but in the other three some lowering has persisted for a year or more. There was no apparent difference in the effects of resecting the right or left thoracic chain. Thus the results in these several patients indicate that there may in some be a greater lowering of blood pressure with more extensive sympathectomy.

The graded sympathectomy in the six patients who had a bilateral thoracolumbar (T7 or 8 to L3) operation one to two years before completion of a total sympathectomy is of added interest. In three of these patients there was no significant decrease in the blood pressure after the thoracolumbar operation; following completion of the total sympathectomy the diastolic pressure was not affected in one, it was lowered twenty mm. but still high in one, while in the third it was lowered 20 mm., so that the highest diastolic pressure was 100 mm. of mercury. In two of the six patients the thoracolumbar operation resulted in moderate lowering of the pressure, and following completion of the total sympathectomy the diastolic pressure was unchanged in one and lowered to normal (120/80) in the other. In one of the six patients the thoracolumbar operation resulted in a normal blood pressure (220/120 reduced to 140/90) and after completion of the total sympathectomy, performed for relief of disagreeable vasospasm in the upper extremities and tachycardia, the pressure was lowered still further (to 110/70).

Therefore, the evidence indicates that total sympathectomy has a greater effect in lowering blood pressure than a lesser resection of the sympathetics in some patients. In this series a poor or mediocre result after thoracolumbar operation was improved in 50 per cent of the patients by adding the excision of the remaining sympathetics. But the fact remains that a total sympathectomy, even when initially performed, does not always lower the resting blood pressure significantly, and indeed may not lower it at all. Additional interesting facts come to light in regard to the effects of graded sympathectomy in the studies with tetraethylammonium chloride, and in a study after bilateral anterior rhizotomy (T12, L1 and 2) was performed in one patient with a total sympathectomy (see following).

Effects on the Heart.—Two important effects on the heart result from the addition of the upper thoracic sympathectomy to the thoracolumbar operation, providing the excision is carried high enough to include the first thoracic (or the stellate) ganglia bilaterally. These effects are abolition or improvement in cardiac pain by interruption of the afferent nerves that traverse the sympathetics, and slowing of the cardiac rate by interruption of the accelerator nerves. It is believed that the nerve fibers for each of these functions traverse the stellate to the fourth or fifth thoracic ganglia bilaterally.

Angina pectoris unquestionably existed in 17 patients of the series. Four of the six patients who came to total sympathectomy a year or more after thoracolumbar operation had angina pectoris. One patient developed his pain after the first operation; but the other three originally had angina and were unrelieved by the operation. This has been a common experience in patients with angina pectoris having thoracolumbar sympathectomy, even in those with lowered blood pressure. In most of the 17 patients the pain occurred chiefly with effort, but in five the pain imposed definite limitations on their activity. The three patients who died all had angina pectoris. All of the 14 who survived were relieved of pain in the chest and arms, and their capacity

for exercise was increased, but three had occasional and moderate pain in the neck and jaws on exertion. One of these had pain in the neck, in addition to pectoral pain, before operation while the other two developed their cervical pain some time after operation. In case the preoperative pain was unilateral the first stage of the operations was usually planned to sympathectomize that side. In support of past experience that unilateral sympathectomy may be inadequate for relief of unilateral angina pectoris, two of these patients developed a similar pattern of pain on the opposite side during the period of delay before the final operation was performed.

Tachycardia and the palpitation that accompanies it have, in those patients who possessed it, been uniformly relieved by total sympathectomy. Several patients had a relative tachycardia before operation, but two of the patients who had previously had a thoracolumbar operation were greatly distressed by these symptoms, particularly on changing from a horizontal to an erect

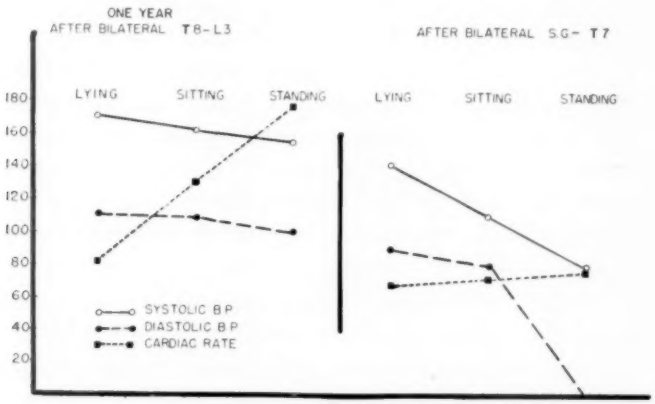

FIG. 2.—Patient No. 25. Effect on tachycardia and blood pressure of adding bilateral upper thoracic sympathectomy (stellate ganglion, S.G., to T7) one year after bilateral thoracolumbar sympathectomy (T8 to L3).

posture, or on exercising. This is a common finding in the early postoperative period after the thoracolumbar operation, when postural hypotension is marked. In a few patients it persists in some degree with change in position, or with exercise, even when postural hypotension has largely or wholly subsided. For example, (Fig. 2) one patient (No. 25) a year after thoracolumbar sympathectomy consistently had a change in blood pressure from 170/110 to 155/100 on rising from a horizontal position, and simultaneously an increase in cardiac rate from 82 to 176 per minute. Paradoxically, during the early period following completion of the total sympathectomy (by bilateral upper thoracic sympathectomy) the blood pressure fell from 140/90 to 80/? on changing posture, and simultaneously the cardiac rate changed from 68 to 76 per minute.

All patients showed bradycardia after completion of total sympathectomy. The rate fell to a level between 40 and 60 per minute, the maximal slowing usually occurring on the second to fourth day after operation. Consistent slowing of the rate was not observed after a unilateral thoracic sympathectomy of either side. While there was some recovery from the maximum bradycardia with the passage of time in most patients, relatively slow resting cardiac rates and failure of tachycardia to develop with postural hypotension or exercise persisted in all patients.

The question of whether cardiac efficiency may be embarrassed when postural hypotension occurs without compensatory increase in cardiac rate may aptly be raised. The studies necessary to settle the question are not completed, but certainly it may be said that after a suitable period of postoperative adjustment passed patients did not show impressive outward evidence of cardiac deficiency under these circumstances.

Other Effects on the Hypertensive State.—The 21 patients with advanced retinopathy, namely, retinal hemorrhages, exudates and papilledema, all showed a subsidence of these changes within one to three months after the completion of any combination of bilateral operation, even though a third stage was sometimes delayed for a longer period. This alteration in eyeground changes is not peculiar to total sympathectomy but occurs also in the less extensive thoracolumbar operation. However, one case in the series (No. 22) developed retinal hemorrhages two years after a thoracolumbar operation, and following the additional operation converting the partial to a total sympathectomy, the hemorrhages subsided.

The improvement in symptoms, particularly headache, seemed to be of the same degree as that reported for less extensive sympathectomies, although it must be said that the average period of convalescence and recovery from operative symptoms took on the average several weeks longer after total sympathectomy than is required after lesser operations. With regard to headache, a suggestion was made, in a report of results after thoracolumbar sympathectomy (Ray[6]), that part of the reason for improvement might be due to a compensatory vasoconstriction of the extracranial branches of the carotids which counteracted the dilatation and lability thought to give rise to headache. After total sympathectomy these vessels should not be in a state of increased tone, but at least should have been deprived of lability in tone which might be expected to be just as effective.

All but two of the patients who survived operation were rehabilitated to the degree that they either resumed wholly or in large part their former occupations and activities, or else led a fairly active existence within moderate restrictions. In Table I, rehabilitation has been indicated as "marked" or "moderate," respectively. By comparison with the evaluation of the degree of their disability prior to operation in the same table, the results are impressive. The two exceptions were both patients who were virtually invalids prior to operation, but neither was made any more so by the operation.

Comparative statistics of survival in a series as small as this and followed for such a short period of time are not truly helpful. Published results[2, 6] of partial sympathectomy show impressive benefit in the matter of survival of patients with advanced hypertension, Groups III and IV retinopathy of the Keith, Wagener & Barker classification, when compared with the latter's published results[7] of survival in similar patients not treated by operation. It will be more important eventually to determine whether more extensive sympathectomy can improve on the results of the thoracolumbar operation. Table III shows certain survival statistics for advanced grades of hypertension the first year after medical treatment,[7] after the Peet operation of bilateral lower thoracic sympathectomy,[2] after bilateral thoracolumbar (T8-L3) sympathectomy[6] and after total sympathectomy. The statistics for the last two types of sympathectomy are from this clinic, and are not significantly different, particularly if the higher operative mortality attending the total

TABLE III.—*Comparison of Percentages of Deaths at the End of One Year in Advanced Hypertension (Groups III and IV Retinopathy) Treated by Different Methods*

		Percentage Mortality at End of 1 Year. Retinopathy Groups		
	No. of Cases	Group III	Group IV	Combined Groups III and IV
Keith, Wagener and Barker				
Medically treated	1 3	35%	79%	69%
Peet				
Lowe thoracic sympathectomy	143	....	46%	...
Ray				
Thoracolumbar sympathectomy	88	10%	18%	14%
Present series				
Total sympathectomy	21	10%	9%	9.5%

sympathectomy were to be taken into consideration, but the results in both these series appear better than those reported following the less extensive Peet operation.

EFFECTS OF THE OPERATION ON HOMEOSTASIS

The coordination of the body as a whole to meet changing conditions in internal and external environment by autonomic adjustment has been called homeostasis by Cannon[8] (1929). Cannon,[8] and McDonough[9] (1939) demonstrated that totally sympathectomized cats and dogs survived under the conditions of the controlled environment of the laboratory, but were unable to make the rapid adjustments which occur in normal animals under conditions of stress, such as extremes in environmental temperature and emotional excitement.

After total sympathectomy in man, the most noticeable effects result from the alteration in vasomotor and sudomotor activity. In the early period after completion of the operation, extremes of temperature are not well tolerated,

and hot weather particularly may be enervating, but by adjustment of clothing and regulation of activity the moderate extremes of temperature occurring in a temperate climatic zone do not afford any great problem in adjustment. The hypotension and its symptoms of giddiness and weakness that accompany change in posture and exercise may be profound soon after operation, and are often of greater degree than that seen following thoracolumbar sympathectomy. There is a sense of obstruction in the nasal passages due to engorgement of the nasal mucosa. The Horner's syndrome may be such that the patient is distressed by his inability to open his eyelids more widely and by the uncomfortable sensation that results from suffusion of the conjunctival blood vessels. Yet within a relatively short time the degree of these symptoms and signs begins to subside and somehow the body makes a progressive adjustment.

The possible means of adjustment are several, and have been commonly thought to be due to sensitization, increase or augmentation in the tone of smooth muscle, and to ready regeneration of sympathetic nerves. Sensitization has been said to occur more readily following postganglionic denervation. In this series there were no discernible differences in the results in the ten patients in whom celiac ganglionectomy was added to the total excision of the ganglionated chains. The possibility that the development of automatic tone in smooth muscle may play some role cannot readily be dismissed, but the bugaboo of regenerating sympathetic nerves needs to be dispelled. The evidence collected from the study of the cases in this series and others gives strong support to the likelihood that the partial return of homeostasis after total paravertebral sympathectomy is due to the presence and augmented activity of residual sympathetic nerves, already present, which do not traverse the paravertebral ganglionated chains, splanchnic nerves or celiac ganglia.

RESIDUAL SYMPATHETIC PATHWAYS

All patients, following paravertebral sympathectomy, whether it is partial or complete, show a predictable loss of sympathetic activity in such measurable functions as skin temperature, sweating, vasodilatation and electrical skin resistance. At first the loss of these functions is complete, but within a matter of days or weeks, long before regeneration of sympathetic nerves could occur, every patient begins to develop recognizable signs of sympathetic activity, which increase with the passage of time and the inherent necessity for the body to utilize whatever compensatory mechanisms remain.

In a previous report[10] residual sympathetic pathways were described innervating the T12 to L3 dermatomes after thoracolumbar (T8 - L3) sympathectomy and also in a few cases after total paravertebral sympathectomy. The matter was explored in considerable detail, and it was shown conclusively that the return of sympathetic activity in these dermatomes, namely in the groins and anterior half of the thighs, could be initially prevented or subsequently corrected if anterior rhizotomy from T12 to L2 inclusive was performed in conjunction with the paravertebral lumbar sympathectomy. This

earlier work raised the possibility that similar pathways were responsible for return of activity in the face, upper extremities, trunk and the lowermost sacral dermatomes. It was postulated that the ganglia for the postganglionic fibers in the residual pathway to the T12 - L3 dermatomes were either in the spinal nerves or closely associated with them. Later it was of great interest to find that the previous work of Wrete[11] and Skoog[12] had already demonstrated microscopic masses of ganglion cells distributed in communicating rami to spinal nerves and often in close proximity to the latter. Even though the function of these ganglia was not established it was believed that they were motor (sympathetic) cells. It was also of interest that the ganglia were found in greatest abundance in the cervical and lumbar regions, although

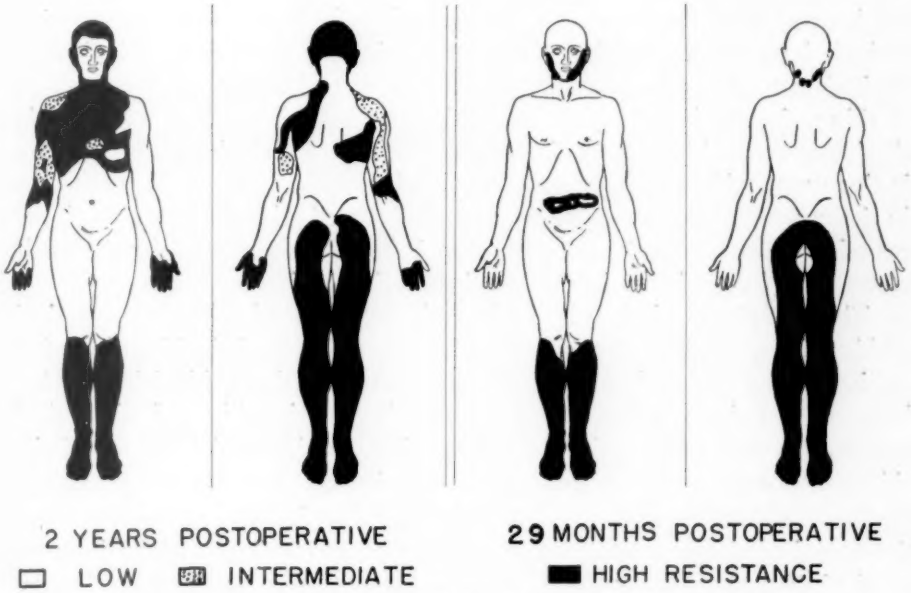

FIG. 3.—Patient No. 8 (Left) Skin resistance pattern 24 months after total sympathectomy. Patient No. 23. (Right) Skin resistance pattern 29 months after total sympathectomy.

similar ganglia were present in all the thoracic spinal nerves. More recently, sympathetic ganglion cells in ventral roots have also been described by Alexander, Kuntz, Henderson and Ehrlich.[13]

Patterns of Skin Resistance.—The patterns of skin resistance over the entire body 24 and 29 months after total sympathectomy in two patients is illustrated in Figure 3. The areas of low resistance indicate the presence of centrally controlled sympathetic activity, and all patients of this series showed similar patterns some months after operation. On the whole, the return of function was most rapid and uniform in the T12 to L3 dermatomes and in the central area of the face, where the patterns were symmetrical and nearly super-imposable from patient to patient. Sympathetic activity returned more

slowly in spotty areas over the upper extremities and trunk, where the patterns were less symmetrical and less constant. The final patterns in the upper extremities and trunk did not conform to any segmental arrangement, and varied considerably on the two sides in the same patient. It does not seem reasonable to attribute this non-segmental and asymmetrical return of function, after similar types of sympathectomy have been performed on the two sides, to sensitization, regeneration or any other of several suggested mechanisms except activation of already existing nerve pathways. Skoog's[12] work has shown that there are marked differences in the number and precise location of the accessory ganglion cells in the cervical region in different patients and on the two sides in the same patient.

Complete and permanent sympathectomy in the upper extremity has not yet been accomplished by any of the operations in common practice, nor has a single instance occurred in which the trunk has remained completely denervated after total sympathectomy. The irregular and inconstant late patterns of skin resistance in the upper extremities are in marked contrast to those in the lower extremities, where the pattern is constant and where rarely if ever is there any evidence of resumed function below the knees. This difference in the upper and lower extremities is in full accord with the common clinical experience that sympathectomy employed for the treatment of vasospastic states is uniformly better in the feet than in the hands.

The usefulness of electrical skin resistance determinations as a method of identifying sympathetic activity has been soundly established by Richter's[14] work. But on the surface areas of the body where the residual innervation is great enough, sweating, pallor, or mottling of the skin and diminished temperature are often easily demonstrated. Sweating and mottling of the skin occur in varying degree in such areas, the degree apparently depending on the number of residual ganglion cells supplying the area, and the need for the organism to compensate for impairment of sympathetic activity in other parts of the body. For example, it is common to see cold hands, pallid fingers, mottling of the arms, and increased sweating in the upper part of the body after thoracolumbar (T8-L3) sympathectomy has deprived lower portions of the body of vasomotor and sudomotor functions. When larger areas are deprived of function by total sympathectomy compensatory activity is greatly augmented in any region where residual innervation exists. This is exemplified by the excessive sweating which occurs in the anterior thighs and groins, particularly during the early months after total sympathectomy. This region (T12-L3 dermatomes) appears to be the most richly supplied by residual pathways of any in the body. Excessive sweating similarly occurs in a band in the lower thorax, if in performing a total sympathectomy a two-stage operation on one side fails to meet and the sixth or seventh thoracic ganglion is left intact, as has occasionally occurred.

It has often been observed though not easily explained that after sympathectomy the resumption of demonstrable sympathetic activity in predictable

areas supplied by residual nerves is delayed in its appearance. Even when a single midthoracic paravertebral ganglion is left in place in an otherwise total sympathectomy the thoracic dermatome supplied by the ganglion appears for several days or weeks to be sympathectomized also. Then, sweating begins to appear, and it increases gradually in amount until the skin of that dermatome may be dripping. This phenomenon more than any other meets the objection of those who maintain that if residual pathways do exist, the evidence of their presence should be manifest immediately after operation.

Other Clinical Evidence.—In at least three patients of this series cramping pains in the anterior thighs developed on exercising after total sympathectomy, even though intermittent claudication had not existed before

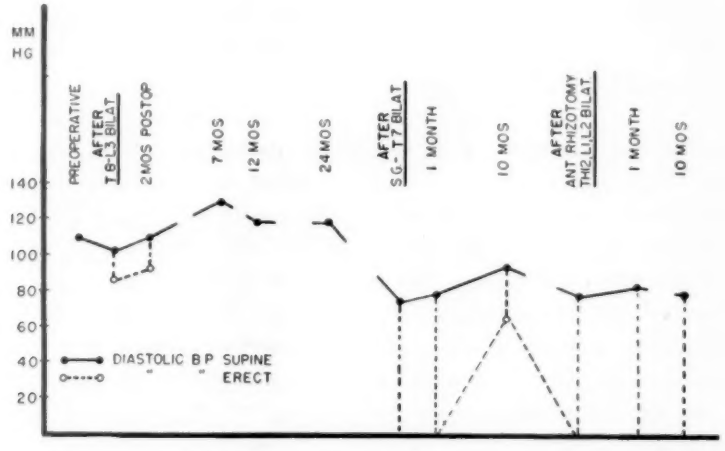

FIG. 4.—Patient No. 24. Effect of graded sympathectomy on blood pressure, particularly emphasizing the additional effect of anterior rhizotomy ten months after total paravertebral sympathectomy.

operation. Since the surface areas of the anterior thighs possess a residual sympathetic innervation it was reasoned that the vasculature of the thigh muscles might be spastic in compensation for extensive vasodilatation elsewhere in the body, and this in turn might lead to pain on muscular effort. Accordingly, in one of these patients (No. 24) anterior rhizotomy, T12 to L2 bilaterally, was performed. At the time of operation direct faradic stimulation of each of these roots caused a transient alteration of skin resistance in the homolateral anterior thigh. The result of the operation was abolition of the cramps as well as loss of sympathetic activity on the surface of the T12 to L3 dermatomes, and the effect may be assumed to be permanent. In this same patient (Fig. 4) the anterior rhizotomy had an additional effect on postural hypotension and to a lesser degree on the blood pressure in the supine position.

The lowest spinal segmental extent of the sympathetic system from this and previous studies has been found to be L3. The highest spinal segmental

extent has not been definitely established, though it has been assumed in the past to be T1 or possibly C8, the rami from which connect with the stellate ganglion. The consistent appearance of sweating in the face after total sympathectomy, including the stellate ganglion, has raised the question as to the mechanism. The question remains unsettled, but there are other experiences to suggest that sympathetic innervation to the pupil and levator of the upper lid has segmental origins above the eighth cervical. As illustration, 18 months after completion of total sympathectomy, including removal of the stellate ganglia, a patient was found to have greater ptosis and miosis on the left side; some degree of asymmetry being common in such cases. The entire remaining cervical sympathetic chain was then removed on the right side, which resulted in a persistent inequality in ptosis and miosis, but now greater on the right side. Unless it be assumed that regenerating preganglionic fibers from thoracic levels joined the cervical chain, which is believed to be unlikely, it must be reasoned that preganglionic fibers arise from cervical segmental levels.

It can probably be shown that preganglionic cervical fibers to the upper extremities which do not traverse the ganglionated chain also exist. This postulation is given support by the finding that following paravertebral thoracic sympathectomy, including the stellate ganglion, supplemented by intraspinal division of the first three thoracic anterior nerve roots, there is still evidence of residual sympathetic activity in the extremity.

In the face of the evidence of the importance of other sympathetic pathways that remain after any type of sympathectomy, including total paravertebral excision, the question which logically follows is what part, if any, such remaining nerves contribute to the failure of sympathectomy to reduce blood pressure in some patients. Also, it must be recalled that whereas the residual nerves that have been demonstrated as not traversing the sympathetic chains all accompany spinal nerves, there are no somatic nerves to the viscera. Unfortunately, there are no methods for accurate detection of residual sympathetic activity in the splanchnic region as there are for the superficial areas of the body. Working with a series of our patients who had thoracolumbar ($T8 - L_3$) or total sympathectomy Swift and Almy[15] have demonstrated that the abnormal eosinophilic response in the blood stream following the administration of insulin does not differ in these two groups of patients. This suggests that splanchnic denervation is no more complete after total sympathectomy than after the thoracolumbar operation, and that any additional effect of the operation must be attributed to other mechanisms.

The idea seems to be held by many that the advantage of sympathectomy lies in some specific effect on the splanchnic vasculature. Others maintain that whatever advantage the operation possesses is in the de-efferentation of the kidneys or adrenals or both. The added effects of lowering blood pressure after each step of a graded sympathectomy would tend to refute this reasoning, particularly when resections at the extremes of the sympathetic chains,

which should largely affect the extremities, result in lower resting blood pressure and increase in postural hypotension (Figs. 1 and 4). Occasionally a bilateral sympathectomy of the lower extremities in a normotensive patient will result in a postural hypotension, and in a small series of patients in whom sympathectomy of all four extremities was performed in rapid succession for Raynaud's disease or hyperhydrosis, postural hypotension of significant degree followed temporarily. The point to be made is that lowering of blood pressure may follow the interruption of any part of the sympathetic system, and whatever part is left functions in the compensatory role of adjustment.

Pharmacologic Evidence.—The following two experiments demonstrate by pharmacologic methods that the interruption of residual sympathetic path-

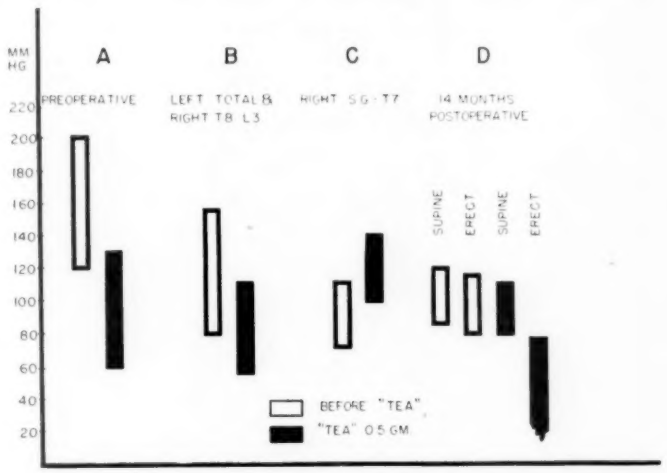

FIG. 5.—Patient No. 17. Effect of T.E.A. on blood pressure (A) preoperatively; (B) after unilateral total and thoracolumbar sympathectomy; (C) shortly after completion of total sympathectomy; and (D) 14 months later.

ways after total paravertebral sympathectomy results in temporary lowering of blood pressure, but the question of whether residual nerves to the splanchnic region exist is not answered.

Tetraethylammonium chloride (T.E.A.)* has the pharmacologic action of blocking autonomic ganglia. While it has not been found useful in predicting the effect of sympathectomy in hypertensives it does provide a convenient method for demonstrating the presence of residual functioning sympathetics. In seven patients who had total sympathectomy performed in three stages, the administration of T.E.A. between the performance of the second and third stages (that is, when all that remained of the sympathetic chains on both sides was the upper thoracic chain from stellate to T7 on one

* T.E.A. was supplied as Etamon by Parke Davis & Co.

side) always resulted in a significant fall of blood pressure. This apparently indicated the importance of the remaining upper thoracic chain in maintaining the level of blood pressure.

When T.E.A. was given in the early period after completion of total sympathectomy in nine patients there was no appreciable change in blood pressure in two, while in seven there was a definite rise in both systolic and diastolic pressures. This response is interesting but the explanation is not definite. More important is the finding that eight to 14 months later, after postural hypotension was lessened and other evidences of residual sympathetic pathways had appeared, the administration of T.E.A. in three patients was followed in each by a slight fall in resting blood pressure and a marked fall on standing.

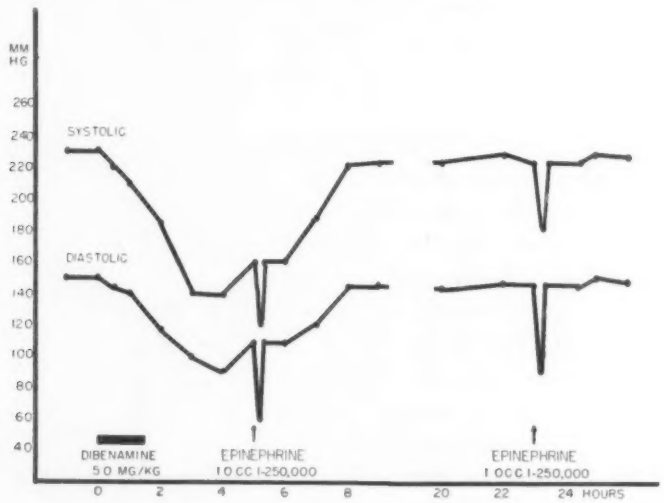

FIG. 6.—Patient No. 8. Effect on blood pressure of dibenamine and "reversal" of epinephrine two years after total sympathectomy.

Figure 5 is a graphic record of the effects of T.E.A. at different periods in the course of observation, before, during and after total sympathectomy, in one patient (No. 17), and it demonstrates the points that have been made in the use of this drug in showing the relation of residual sympathetic pathways to the maintenance of blood pressure.

Dibenamine* (dibenzyl beta-chloroethylamine hydrochloride) like T.E.A. may cause a fall in blood pressure, but through a different pharmacologic action. It is believed to have a combined effect of producing a sympathetic paralysis of the neuro-effector cells peripherally and of neutralizing epinephrine; that is, its action is both sympatholytic and adrenolytic. Since much has been said about the probable action of vasopressor substances, particularly

* Dibenamine was supplied by Givaudan-Delawanna Inc., Delawanna, N. J., through the courtesy of Dr. W. Gump.

circulating epinephrine, in maintaining blood vessel tone and an elevated blood pressure in some hypertensives, dibenamine seemed an ideal drug for testing the role of epinephrine in a patient (No. 8) who had a sustained hypertension two years after total sympathectomy (Fig. 6). When dibenamine was given there was a prompt fall in blood pressure, due presumably to the dual action of the drug on residual sympathetic nerves and on circulating epinephrine. Before the blood pressure returned to its initial level the administration of epinephrine caused a new fall in blood pressure, which was a reversal of the effect which might have been expected. But most important was the observation that 15 hours after return of the blood pressure to its initial level a repeat injection of epinephrine again showed a reversal of the normal reaction. From this it is suggested that circulating epinephrine is not the factor that maintains an elevated blood pressure after total sympathectomy, but that residual sympathetic activity or some other unknown factor is.

CONCLUDING REMARKS

The justification for employing sympathectomy in the treatment of hypertensive vascular disease still suffers for lack of an understanding of the etiology of the disease, and of the mechanism by which the operation is sometimes beneficial. The maintenance of systemic blood pressure is a physiologic mechanism which does not differ basically from other homeostatic mechanisms controlled by the autonomic nervous system. Whether essential hypertension is primarily an extreme expression of this function, or whether some other and essentially unrelated factor supervenes, evades many efforts at detection. Furthermore, for lack of evidence, there is disagreement concerning the significance or the role of the elevated blood pressure in the disease. Sympathectomy has never been anything more than an empirical therapeutic effort, but as such there is ample evidence that it often lowers blood pressure and results in measurable benefits to the patient.

For those who are occupied with the performance of the surgery there have been changing ideas regarding the necessity and the safety of increasingly extensive sympathectomy. More information was needed on whether complete removal of the paravertebral ganglionated chains would improve on the shortcomings of lesser operations and, just as important, whether the organism could survive this loss without serious limitations. The study of the patients of this series has provided some of the answers.

The evidence indicates in some measure that there is a quantitative relationship between the extent of the sympathectomy and degree of lowering of the blood pressure. This apparently has nothing to do with the more complete or permanent denervation of any specific region such as the splanchnic area, but is related to a more widespread vasomotor paralysis. Even so, the percentage of improved results in the blood pressure lowering effect is hardly great enough to justify the somewhat greater morbidity and mortality which

attend the total sympathectomy when compared with a lesser operation such as the thoracolumbar T7 or 8 to L3, and splanchnic nerve resection.

There are advantages to the total sympathectomy, however, in that it deafferents and decellerates the heart. It also improves vasospastic states in the extremities which, if not initially present, may become a source of concern after less complete sympathectomy. These effects would seem to constitute the chief, if not the sole, justification for extending the sympathectomy above the mid-thoracic level.

That total paravertebral sympathectomy from the stellate to the third lumbar ganglia does not imply *complete* sympathectomy is impressively established by the evidence of residual sympathetic activity via nerve pathways which do not traverse the ganglionated chains. It is the presence of these residual nerves, augmented in their activity by the demands of the organism to compensate for what has been lost, that maintains some degree of homeostasis and, too, may also compromise the effect of the operation on the level of blood pressure.

It is concluded then, that:

1. Total paravertebral sympathectomy from the stellate to the third lumbar ganglia accomplishes a somewhat greater blood pressure lowering effect than does the less extensive thoracolumbar (T7 or 8 to L3 and splanchnic nerve) sympathectomy. However, it does not appear that for this purpose alone there is enough advantage to the former to justify its use except in special circumstances.

2. The special circumstances include chiefly, angina pectoris, tachycardia and vasospastic states in the extremities. In these conditions total sympathectomy has demonstrated its worth.

3. Homeostasis has not been significantly threatened by the operation, and after a period of readjustment patients are able to lead relatively normal lives within the limits of extreme demands on the body.

4. Much of the preserved homeostasis, as well as other evidences of persistent sympathetic activity after total sympathectomy, is believed due to the existence and augmented activity of sympathetic nerves that are not interrupted by the operation.

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DISCUSSION.—DR. REGINALD H. SMITHWICK, Boston, Mass.: I think Dr. Ray and I agree pretty completely on most aspects of the surgical treatment of hypertension. I would like to state my feelings about total sympathectomies as briefly as possible.

In investigating the problem of hypertensive cardiovascular disease and its treatment by sympathectomy, it has been my policy to commence with the least extensive procedure which might be helpful and, having evaluated the result, then to extend the maneuver if nothing worthwhile seemed to have been accomplished.

Having observed the response to subdiaphragmatic or supradiaphragmatic splanchnicectomy in groups of patients, the operation was extended in failures to a combined maneuver by reoperating upon the same individuals and increasing the extent of the maneuver either upward or downward. Because it was possible to increase the percentage of early successes by about 30 per cent without adding unduly to the morbidity or mortality, the combined procedure, called lumbodorsal or thoraco-lumbar splanchnicectomy, was adopted as a standard procedure a little over ten years ago.

In approaching the question of total sympathectomy the same plan has been used, namely, to extend the operation in failures following thoracolumbar sympathectomy to total sympathectomy in subsequent stages. Over a period of 12 years I have performed total sympathectomy in 16 patients. I have not been impressed by any additional benefit to the patients either with regard to blood pressure levels or the further abolition of reflex vasomotor elevations of blood pressure as judged by the Valsalva maneuver.

I have been impressed by the fact that four of the 16 totally sympathectomized patients were totally disabled for long periods of time because of their inability to stand, having lost both their capacity to constrict the splanchnic bed and to accelerate the heart rate. This is demonstrated by the first slide.

It is my belief that total sympathectomy should never be performed as a primary procedure in hypertensive patients. The morbidity and mortality will be too great, aside from the probability that it is unnecessary. Also, the success or failure of surgery

of this sort depends upon many factors other than the extent of operation—particularly the amount of cardiovascular damage which exists at the time of operation.

My experiences with thoracolumbar splanchnicectomy have led me to believe that there are two groups of patients who should not be treated in this fashion, namely, those with coronary heart disease and angina pectoris, and those with postural tachycardia. These, I feel, are best treated by a transthoracic sympathectomy, removing the chains bilaterally from the inferior cervical to the twelfth thoracic ganglia in the former, and from the second thoracic to the twelfth ganglia in the latter group. These operations are performed at present in about 15 per cent of the patients, and with thoracolumbar procedure in about 85 per cent of patients.

I personally do not feel that it is necessary to do a total sympathectomy as a primary procedure in patients with hypertension and angina pectoris or tachycardia.

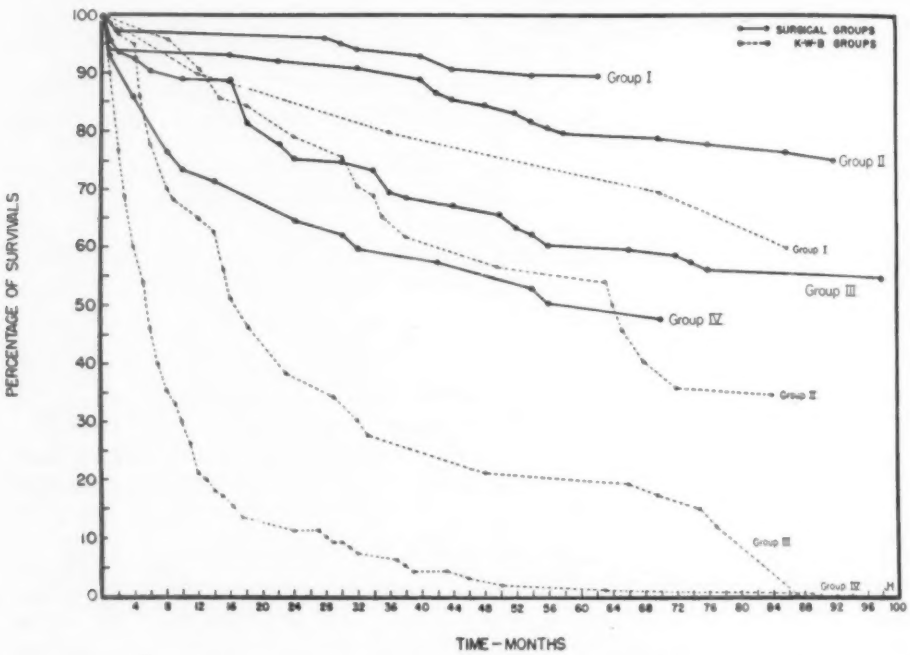

FIG. 1.—Survival curves following lumbodorsal splanchnicectomy; 209 cases followed five to nine years arranged according to Keith, Wagener and Barker Groups and compared with their 219 cases followed five to nine years.

I should like to say a word about the value of splanchnicectomy in the management of hypertensive cardiovascular disease. This, in the last analysis, will be judged by its effect on the progress of cardiovascular disease and upon life expectancy. We now have a sufficient number of consecutive, unselected cases followed for a sufficient length of time after lumbodorsal splanchnicectomy to indicate that the progress of cardiovascular disease has been slowed, and life expectancy increased to a statistically significant degree.

This is indicated by a comparison of the survival curves of our patients with those of Keith, Wagner and Barker, of the Mayo Clinic. Their data for medically treated patients, published in 1939, stands today as the best available standard by which to judge the efficacy of any form of treatment for hypertensive cardiovascular disease.

The illustration shows the survival curves of Keith, Wagner and Barker for a group of 219 unselected hypertensive patients divided into four groups according to the severity

of the changes in the eyeground. There are minimal vascular changes in Group 1, sclerotic changes in Group 2, hemorrhage or exudate and vascular changes in Group 3, and the so-called malignant hypertensives in Group 4, patients who generally have hemorrhage and exudate and always papilledema. The percentage of survivals that you see depends upon the severity of the disorder at the time of the beginning of the period of observation; and particularly, in Groups 3 and 4, by the end of about seven years all of the patients are dead.

The figure also shows our survival curves for the first 299 consecutive unselected cases which were treated by thoracolumbar splanchnicectomy, and divided into comparable groups. The difference between the two series is very striking. It is highly significant on statistical analysis for Groups 2, 3 and 4.

It is my belief that if one performs the right type of operation at the proper stage of the disorder, surgery is of real value in the management of this disease. This would exclude the use of total sympathectomy as a primary procedure and the use of surgery of any sort in the terminal or near terminal stage of the disease.

THE USE OF BACITRACIN IN EXPERIMENTAL *CLOSTRIDIUM WELCHII* INFECTION IN GUINEA PIGS*

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THE LABORATORY EXPERIMENTS reported in this paper were conducted to determine the value of the antibiotic, bacitracin, as a prophylactic agent against *Clostridium welchii* infection in guinea pigs.

In May, 1943, while studying the bacterial flora of badly contaminated civilian accidental wounds, Johnson, Anker and Meleney discovered an organism which produced a powerful antibiotic agent.[1] The organism is a gram-positive, spore-forming aerobic rod and it belongs to the *Bacillus subtilis* group. The antibiotic has been named bacitracin. It possesses a wide range of antibacterial activity. It is effective, in vitro, against gram-positive organisms such as streptococci, pneumococci, staphylococci, micrococci, corynebacteria and clostridia, and against two species of gram-negative organisms, gonococci and meningococci. It is ineffective against gram-negative aerobic rods such as members of the coliform, proteus, and pyocyaneous groups. Spirochetes are highly susceptible, but fungi, such as monilia and cryptococci, are resistant.

Johnson, Anker, Scudi and Goldberg[2] reported the first observations on the use of bacitracin in clostridial infections in animals. Guinea pigs were protected against the development of gas gangrene when *Clostridium welchii* or *Clostridium septicum* was the infecting organism. Eighty to 90 per cent of the animals survived when an 18-hour culture of *Clostridium welchii* was injected into the thigh muscles in the amounts of 0.5 to 0.25 cc. and bacitracin was injected immediately subcutaneously, followed by subsequent doses every 3 hours for 36 to 72 hours. The first dose was 400 units, the second dose 200 units and the remaining doses 100 units. Some swelling of the leg occurred in the treated animals, but after 12 to 18 hours this subsided completely. All of the untreated control animals died within 24 hours. When a similar dosage of bacitracin was given after a 3-hour delay between contamination and the first treatment with bacitracin, the animals were not protected.

Similar studies with bacitracin in experimental clostridial infection have been conducted by Altemeier.[3] Animal wounds containing crushed muscle and sterile dirt were contaminated with one M.L.D. of *Clostridium welchii*. The animals were treated with 2000 or 8000 units of bacitracin per kilogram daily, divided into doses given at 4-hour intervals. The result of this experi-

ment showed that bacitracin had a definite prophylactic and therapeutic effect on these infections.

METHODS

In a previous communication[4] it was pointed out that it was highly desirable to devise experiments in which clostridial infections in animals simulate as closely as possible clinical gas gangrene in human beings. In the experiments which are to be described in detail, wounds were produced in anesthetized guinea pigs and contaminated with *Clostridium welchii* which is the organism most frequently associated with clinical clostridial infections in human beings. The study was conducted so that in each experiment one group of animals received a wound and a contaminating inoculum, but was given no bacitracin, and the animals serving as controls, while another group of animals comparable in number and in weight received a wound, an identical contaminating inoculum, and bacitracin. In principle the method used to produce the experimental lesion is that described in 1940 by Legroux.[5] The object of this investigator was to produce in guinea pigs lesions simulating war wounds contaminated with clostridia and to treat them with chemotherapeutic agents.

In the study herein reported guinea pigs were used as the experimental animals. Their weights ranged from 294 to 1038 grams; however, the usual weight in any given experiment ranged from 325 to 550 Gm. The hair was removed from both hindquarters by clipping. The animals were anesthetized with sodium pentobarbital administered subcutaneously in the form of a 1 per cent solution in distilled water. Three and one-half to 4 cc. of this solution per kilogram of body weight produced satisfactory anesthesia. The skin of one hindquarter and leg was scrubbed with a brush, using soap with an added chemical* and water, after which this area was sprayed with an antiseptic solution.† The operation was performed under aseptic technic. A skin incision 1 cm. in length was made over the gluteus maximus muscle of the animal. After this muscle was exposed, a portion of it was traumatized by crushing with a Kocher clamp. An effort was made to achieve uniformity in the size of the incision and the degree of trauma. The skin wound was then closed with non-absorbable suture material and covered with collodion, which was allowed to dry. The latter two steps were performed to reduce the probability of secondary contamination of the operative wound, to prevent loss of the bacterial inoculum, and to insure an anaerobic environment in which the organisms could multiply. Finally the wound was contaminated by injection of bacteria through the adjacent normal skin into the traumatized muscle, using a hypodermic needle and syringe.

Actively growing vegetative forms of *Clostridium welchii*‡ cultured in cooked beef heart medium were used in the dosage recorded below to contami-

* Bis-(3,5,6-trichloro-2-hydroxyphenyl)methane.

† Formula: $HgCl_2$ 0.7 Gm. tricresol 5 cc., acetone 100 cc., alcohol (95%) 525 cc., water 375 cc.

‡ The organism used was obtained from Dr. Frank L. Meleney, of New York, who had originally obtained it from Dr. Ivan C. Hall. It is identified as Strain 1929.

nate the wounds. Before each experiment a gram-stained smear of the culture was made for the purpose of determining the purity of the culture. At the same time a serial dilution of a portion of the culture was made to determine the highest dilution in which the organism could be grown. This value for the 33 separate experiments was as follows: 10^{-4} in 2 experiments; 10^{-7} in 2; 10^{-9} in 12; 10^{-10} in 9; 10^{-11} in 5; and 10^{-12} in 3.

In one experiment in which 0.1 cc. of a 12-hour culture was used, only four out of 11 control animals died of clostridial infection; however, all six of those that survived the 15-day period of observation showed evidence of clostridial

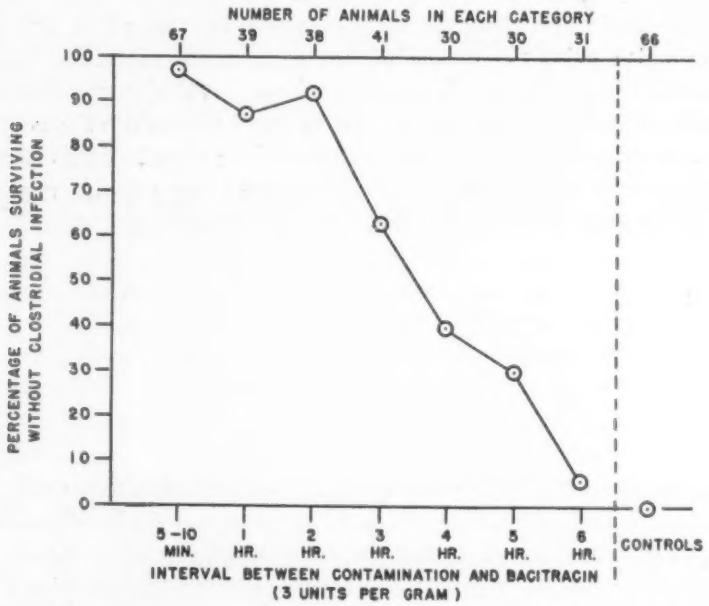
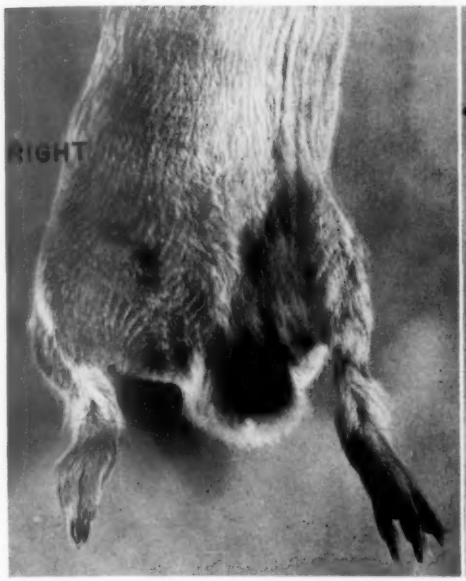


FIG. 1.—A graph to show the percentage of animals surviving for 15 days without evidence of clostridial infection in those experiments (See Table III) in which the administration of bacitracin was delayed for varying intervals of time following wound contamination. The contaminating inoculum consisted of 0.1 cc. of a 4 to 6½ hour culture of *Clostridium welchii*. Bacitracin (Lot No. B480420) in the amount of 3 units per gram was given to one group of animals. Another group served as controls.

infection. After this experiment the inoculum was increased to 0.2 cc. and in four experiments performed with this inoculum 20 out of 33 control animals died of clostridial infection. Of the 13 animals that survived the 15-day period of observation all showed evidence of clostridial infection. Because of dissatisfaction with the results of these early experiments, the inoculum was further altered, and in the remaining experiments a 4 to 6½ hour culture was used and 0.1 cc. was administered. The results became highly satisfactory and among 180 control animals 173 died of clostridial infection. Of the 173 animals 88 per cent died within 72 hours of the contamination. All of the seven animals



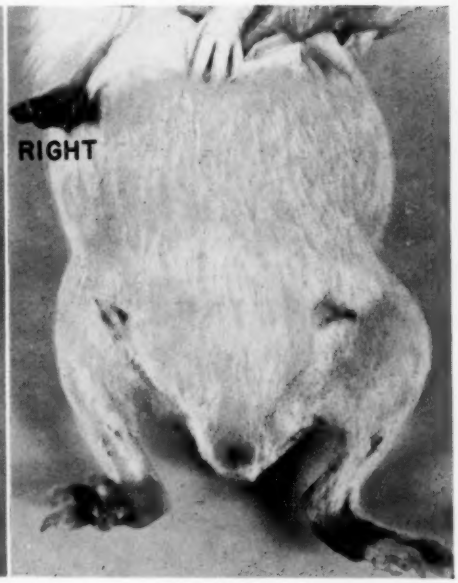


FIG. 2 FIG. 3

FIG. 2.—Photograph of a control animal taken shortly after death 20 hours following wounding and contaminating with 0.1 cc. of a culture of *Clostridium welchii*. Note the extensive edema and discoloration of the right thigh, groin and lower portion of abdomen.

FIG. 3.—Photograph of an animal wounded and contaminated at the same time as the one in Figure 2, but one that received bacitracin in the amount of 2 units per gram shortly after contamination. Note normal appearance of the wounded right leg. This animal survived the 15-day period of observation.

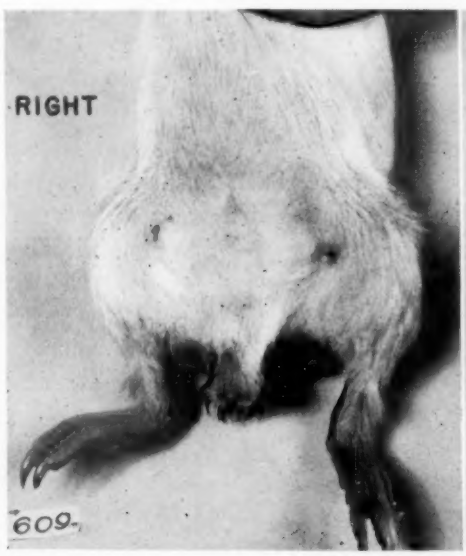


FIG. 4.—Photographs (anterior and posterior views) of an animal that was given bacitracin in the amount of one unit per gram shortly after receiving a wound contaminated with *Clostridium welchii*. This animal survived 17 days at which time he was photographed, sacrificed and autopsied. There was no evidence of clostridial infection. Note the small crust covering an otherwise cleanly healed wound.

that survived the 15-day period of observation showed evidence of clostridial infection. A mortality rate of this magnitude obviously offers an adequate challenge to the antibiotic.

Bacitracin* was dissolved in physiologic saline solution and administered intramuscularly in varying dosages. The dosage was calculated on the basis of the weight of the animal, and in this report is expressed in units per gram.

In three groups of experiments the antibiotic agent was given 5 to 10 minutes after contamination of the wound except in one experiment in which the

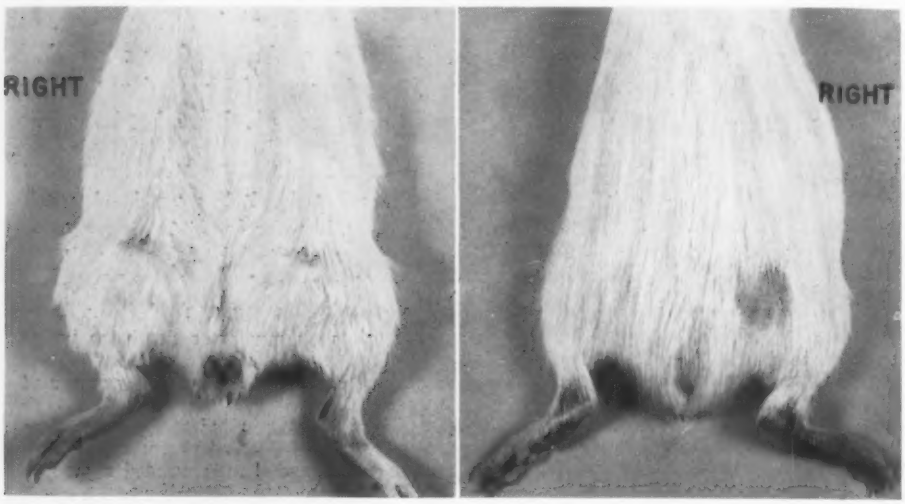


FIG. 5.—Photographs (anterior and posterier views) of an animal that was given bacitracin in the amount of 3 units per gram shortly after receiving a wound contaminated with *Clostridium welchii*. This animal survived 17 days at which time it was photographed, sacrificed and autopsied. Note the completely healed operative wound. (The hairless area in the photograph on the right.)

interval was 20 minutes. The amount of drug administered in the different experiments varied, ranging as follows: 1.66 units per Gm. every 4 hours until 18 injections had been given; 3.3 units per Gm. every 4 hours until 3 injections had been given; and finally single injections in amounts of ½, 1, 2, 3 and 10 units per Gm.

In a fourth group of experiments the administration of bacitracin was delayed following contamination of the wound but the dosage was kept at a constant of 3 units per gram. The interval between contamination and administration of the drug ranged from 5 to 10 minutes up to 6 hours.

During the postoperative period each animal was kept in a separate cage and offered a diet consisting of commercially prepared food pellets, fresh vegetables and water. The animals were observed at frequent intervals and notes were made concerning their general state of health and the appearance of the local

* The bacitracin used in these experiments was supplied by Commercial Solvents Corporation of Terre Haute, Indiana.

lesion. Every animal that died was subjected to a postmortem examination, and cultures were obtained from the tissue exudate in almost all of those that showed gross evidence of infection. All surviving animals were kept under observation for 15 days.

RESULTS

When infection occurred following wound contamination the clinical course of the guinea pigs and the gross pathologic lesions were characteristic. The animal developed swelling in the region of the wound which promptly spread, so that the ipsilateral thigh was soon included. Usually before the animal died the process involved the groin and the abdominal wall, and in some instances the thoracic and even the cervical regions. The swelling became noticeable in the region of the wound and in the wounded leg in approximately 12 hours and often reached the abdominal or thoracic walls within 18 to 24 hours. Most of the animals that survived infection for as long as 72 hours developed skin necrosis in the area immediately surrounding the site of operation. In some this necrosis was even more widespread, involving areas on the leg, groin or abdominal wall. The infected animals looked ill. They were listless, inactive, and ate poorly. These signs progressed with the passage of time. At postmortem examination, made in all fatal cases, in the area immediately surrounding the wound, the muscle was invariably pale, avascular and necrotic, and often liquefied. Beyond this zone there were hemorrhagic congestion and edema of the muscle. In the adjacent subcutaneous tissue spaces there was an exudate more often serosanguineous, but occasionally slightly gelatinous. This was often extensive, and seemed to accumulate in pockets in association with gas. Cultures taken from this exudate consistently yielded *Clostridium welchii*. Every control animal developed the lesions of clostridial infection; however, some recovered despite the fact that the process ultimately reached an advanced stage. These animals showed during the 15-day period of observation the same type of swelling as those which died, and showed also subsequent spontaneous wound disruption, with the discharge of foul-smelling purulent material, and finally, ulceration and crust formation. When sacrificed and autopsied, there

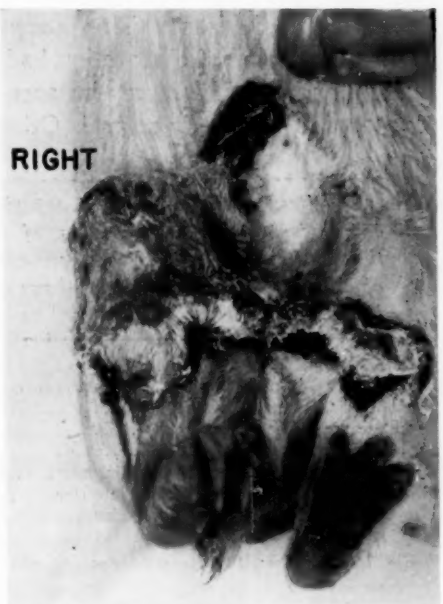


FIG. 6.—Photograph of a control animal 14 days after wounding and contamination with *Clostridium welchii*. Note the extensive amount of crust, ulceration and gangrene. This is one of a small number of control animals that survived the 15-day period of observation. It showed evidence of clostridial infection at autopsy.

were varying degrees of muscle injury ranging from complete dissolution to slight superficial necrosis. Figure 6 is an illustration of such an animal.

In the majority of the animals that did not develop active infection there was primary healing of the wound. In a few instances the operative wound became superficially ulcerated, but in no way showed any of the characteristics of clostridial infection. Some animals among those receiving bacitracin showed local reactions which took the form of swelling involving the ipsilateral leg or even the abdominal or thoracic walls. This usually appeared by the end of the first 18 to 36 hours after operation and gradually subsided within the next 24 to 48 hours. This reaction apparently did not result in permanent change. When the period of observation had terminated these animals were sacrificed and autopsied, and in every instance the region previously the site of swelling appeared to be entirely normal. Other animals in the bacitracin group survived

TABLE I.—*Results of the first five experiments in which there was a high survival rate among control animals and a loss of numerous bacitracin animals due to causes other than clostridial infection. In these experiments the contaminating inoculum consisted of either 0.1 or 0.2 cc. of a 12-hour culture of Clostridium welchii. Bacitracin (Lot No. B471231S) was administered as indicated above.*

	Bacitracin				Controls
Units per Gm. in each injection	1.66	3.3	10	5	..
Number of injections	18*	3*	1	1	..
Total dosage of bacitracin in units	30	10	10	5	..
Total number of animals	19	44	15	15	44
Survived without evidence of clostridial infection	5	37	12	14	0
Died of causes other than clostridial infection	14	7	3	1	0
Survived but showed clostridial infection	0	0	0	0	20
Died of clostridial infection	0	0	0	0	24

*First injection 5-10 minutes after wound contamination; subsequent injections every 4 hours.

the 15-day period of observation, but showed, as is described above, changes compatible with clostridial infection. All such examples occurred among those animals receiving 2 units or less of bacitracin per gram at the time of contamination or among those receiving 3 units per gram given after the lapse of an interval of time.

A total of 747 guinea pigs was used in this study. Thirty-three separate experiments were performed, each involving from four to 38 animals. The results of these experiments are recorded in Tables I, II, and III. These tables are based on observations made on 724 animals, 23 animals having been excluded from consideration. Each of the animals excluded had been anesthetized, operated upon, and the wound had been contaminated, but each died within the first 12 postoperative hours, never having recovered from anesthesia. The exclusion of such animals seems justified, since none had developed clinical evidences of clostridial infection by the time of death.

In the first five experiments (Table I) the mortality rate among the control animals was too low to offer a sufficiently critical test for the antibiotic agent. Moreover, a large number of the animals treated with bacitracin died of

causes other than clostridial infection. Therefore no conclusion can be drawn from this group of experiments.

The results in the remainder of the experiments are decidedly more conclusive. Those experiments in which bacitracin was given shortly after wound

TABLE II.—*Results of experiments in which bacitracin (Lot No. B480420) was administered between 5 and 10 minutes after wound contamination. The contaminating inoculum consisted of 0.1 cc. of a 4 to 6½ hour culture of Clostridium welchii. The controls received a contaminating inoculum but no bacitracin.*

	Bacitracin Amounts in units per gram				Controls
	3 Units	2 Units	1 Unit	0.5 Unit	
Total number of animals	51	22	33	25	114
Survived without evidence of clostridial infection	50 (98%)	19 (86%)	25 (75%)	6 (24%)	0 (0%)
Died of causes other than clostridial infection	0	1	3	2	0
Survived but showed clostridial infection	0	0	4	7	2
Died of clostridial infection	1	2	1	10	112

contamination are summarized in Table II. From this table it can be seen that among 114 control animals every one developed clostridial infection and only two survived the 15-day period of observation. When bacitracin in the amount of 3 units per gram of the animal's body weight was given to 51 animals, 98 per cent showed no evidence of clostridial infection and survived. When smaller

TABLE III.—*Results of experiments in which varying intervals of time were allowed to lapse between wound contamination and the administration of bacitracin. The contaminating inoculum consisted of 0.1 cc. of a 4 to 6½ hour culture of Clostridium welchii. Bacitracin (Lot No. B480420) in the amount of 3 units per Gm. was given to one group of animals. The remainder served as controls.*

	Interval between wound contamination and administration of bacitracin							Controls
	5 to 10 Minutes	1 Hour	2 Hours	3 Hours	4 Hours	5 Hours	6 Hours	
Total number of animals	67	39	38	41	30	30	31	66
Survived without evidence of clostridial infection	65 (97%)	34 (87%)	35 (92%)	26 (63%)	12 (40%)	9 (30%)	2 (6%)	0 (0%)
Died of causes other than clostridial infection	2	4	0	1	1	0	0	0
Survived but showed clostridial infection	0	1	1	3	7	4	2	5
Died of clostridial infection	0	0	2	11	10	17	27	61

amounts of the agent were given the figure for survival without evidence of clostridial infection decreased, being 86 per cent, 75 per cent and 24 per cent for 2, 1 and ½ units respectively.

The experiments in which an interval of time was allowed to lapse between drug administration and wound contamination (Table III and Figure 1) clearly demonstrate that delay in administration of the drug beyond two hours significantly reduces its effectiveness.

DISCUSSION

Although the clostridial infection produced by the method herein described simulates clinical gas gangrene in human beings, it is not identical with it. There are a number of differences. The contamination in these experiments was undoubtedly proportionately more massive than that usually occurring in traumatic wounds in human beings. Moreover, the organisms entered the wound in an actively multiplying state, whereas in the usual clinical wound the contaminating clostridia enter in the spore form. Thus, for comparable intervals following contamination, the experimental lesion is apt to be further advanced bacteriologically than is the clinical wound. Gas gangrene in the human being is usually polymicrobial whereas in these experiments only one organism was used. In the mixed flora of the clinical case there may be organisms which produce substances that inactivate an antibiotic otherwise effective against the clostridial flora of the wound. This may be one element in the explanation of the efficiency of penicillin in certain cases of clostridial infection and its relative ineffectiveness in others.[6] With but one known exception,[7] the action of bacitracin is not influenced by the products of bacterial metabolism.

The usefulness of bacitracin is limited by evidences of toxicity which have been reported.[8-12] Thirty-nine out of 500 animals receiving bacitracin in the study herein reported died of causes other than clostridial infection. These animals either had diarrhea during life or showed pneumonia at autopsy. There appear to be at least two possible explanations: (1) These processes are primary conditions and represent intercurrent infections, or (2) They are secondary terminal manifestations of a primary process which may be some form of drug toxicity. In favor of the former explanation is the fact that during the period in which this high mortality rate was occurring a great many animals in the stock guinea pig colony were also found dead. Unfortunately these were not autopsied and there is no explanation for the causes of their deaths. Moreover, the susceptibility of guinea pigs to intercurrent infections is well known. In favor of the second explanation, namely, that the deaths were due to drug toxicity, is the fact that the mortality rate closely parallels the total amount of bacitracin administered. It is noteworthy that observations[11-13] have been made which indicate that Lot B451231S of bacitracin is more toxic than Lot B480420.

Renal changes have been reported[8, 9] in laboratory animals receiving bacitracin. In view of this observation, kidney tissue has been saved from a number of the animals that died of causes other than clostridial infection. Microscopic study revealed that many of those that received bacitracin in the total amount of 30 units per gram showed necrosis of the epithelium of the convoluted tubules.

There is hope that the disadvantage of toxicity may be overcome, and if it is, a potent agent will be added to the ever increasing antibiotic armamentarium against surgical infections. At the present time adequate and early surgical debridement is the most effective means of prophylaxis, and early diagnosis and

prompt surgical extirpation of the diseased tissues the most effective therapy for clinical gas gangrene. Other measures, such as antitoxin, transfusion and chemotherapy are useful and necessary adjuncts, but in the search for the ideal chemotherapeutic agent with which to combat clostridial contamination and infection one must not lose sight of the fact that surgery remains our most effective weapon.

SUMMARY AND CONCLUSIONS

Experiments were conducted in which wounds were produced in anesthetized guinea pigs and contaminated with *Clostridium welchii*. Untreated control animals developed lesions simulating clinical gas gangrene in human beings.

Bacitracin, an antibiotic derived from a gram-positive spore-forming rod of the *Bacillus subtilis* group, was used as a prophylactic agent and administered intramuscularly.

The first five experiments involving 137 animals gave inconclusive results because of a high survival rate among control animals and a loss of numerous treated animals due to causes other than clostridial infection.

In subsequent experiments involving 245 animals there were 114 control animals of which all but two died of clostridial infection. Among 51 animals that received bacitracin in the amount of 3 units per gram, shortly after wound contamination, 98 per cent showed no clostridial infection and survived the 15-day period of observation. Amounts less than 3 units were less effective.

Experiments involving 342 animals in which the bacitracin dosage was 3 units per gram administered at varying intervals following wound contamination, showed that delay in administration of the drug beyond 2 hours significantly reduces its effectiveness.

These experiments indicate that 3 units per gram of body weight is an effective dose of bacitracin, and when administered at the time of wound contamination is capable of protecting guinea pigs against *Clostridium welchii* infection. When the interval between contamination and drug administration is lengthened beyond 2 hours the prophylactic effectiveness of the drug diminishes with each hour and is completely lost by 6 hours. Due to differences between the infection in the experimental animal and the human being, these results must be applied with caution to the clinical problem. However, they do suggest that when bacitracin becomes available in a form which can be given with safety it may be a valuable adjunct to other well recognized forms of treatment in clinical gas gangrene in the human being.

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DISCUSSION.—DR. EDWIN P. LEHMAN, Charlottesville, Va.: I have been greatly interested in following this work with bacitracin. There is no question of the fact that these observations have proved its efficacy as a prophylactic in experimental *Clostridium welchii* infection in the animal.

I should like to re-emphasize the point that Dr. Sandusky has made, namely, that, up to the present time, at least, any antibiotic therapy, including bacitracin, must be considered solely as an adjunct to surgical treatment in accordance with established principles. Even such striking results as those just presented do not indicate the use of bacitracin instead of surgery. This point must be stressed repeatedly in teaching, although of course it does not need stating before this audience.

Furthermore, it should be repeated that the present status of preparation of this substance does not yet permit its general use by systemic administration in the prevention or treatment of human *Clostridium welchii* infection. There is reason to predict that it would prove as effective in the human being as in the animal if it were permissible to use it.

At the present time the problem of its toxicity is under intensive study, and it now seems possible to get batches of the drug which show little or no toxicity. Until the toxic factor can be reduced consistently or eliminated during the preparation of bacitracin, the latter cannot be made generally available for systemic use, although it has been released for local administration in human beings.

I should like to emphasize also one other point in regard to bacitracin which Dr. Sandusky did not have time to make. Bacitracin has been shown by others to be inactivated by the products of bacterial metabolism in the case of only one known organism. In this respect it differs from penicillin, which is so frequently inactivated by penicillinase. When it becomes permissible to use it in the clinical case it should therefore theoretically be effective when the infection is one of *Clostridium welchii* with variously mixed other flora, as in the usual case of human gas gangrene.

Dr. Sandusky is continuing work with bacitracin using other organisms of the clostridial group. He also has started studying aureomycin and chloromycetin. Results with aureomycin in preliminary experiments in animals, using the same technic as he has described, are encouraging. He has found that chloromycetin is effective in vitro against the clostridia. The animal experiments have not been sufficient in number to allow any pre-

diction about the effectiveness of chloromycetin against *Clostridium welchii* in the living organism.

DR. FRANK L. MELENEY, New York, N. Y.: When I looked over the program of the meeting, I was particularly impressed with the fact that only two of the papers have to do with infections. This shows perhaps how far we have come in recent years in bringing infection under control.

But there are still a few problems of infection which have not yet been solved, and I believe that gas gangrene is one of them. Those who saw gas gangrene during the war (and I believe Dr. DeBakey can give us the figures) realize that the problem of gas gangrene was not solved by penicillin or the sulfonamides.

I have not seen a case of gas gangrene in the last two years, probably because our hospital has no ambulance service, and particularly avoids the admission of street accidents, including gunshot wounds and compound fractures in which gas gangrene is so prone to develop. However, if we have another war, which God forbid, gas gangrene will be a major problem among the victims of atomic bombs, and until we have peace established we must prepare for that eventuality.

I am glad that Dr. Sandusky has been able to continue his studies on experimental gas gangrene, so well begun before the war, when he was trying to evaluate the sulfonamides in the treatment of this disease. These experiments which he has done recently seem to indicate that bacitracin can prevent the development of this disease in guinea pigs if given in time and in sufficient quantities. They suggest that it may be a valuable adjunct to the accepted forms of treatment in clinical gas gangrene in human beings.

The question arises as to whether the presently available bacitracin is safe to use in large enough doses to be effective. That is the feature of Dr. Sandusky's paper that I wish to discuss.

It was thought that bacitracin might be worthy of consideration for Dr. Sandusky's studies in the treatment of gas gangrene when we studied its antibacterial spectrum and found that it was active against a wide variety of organisms, and was particularly active against the gas gangrene group. Furthermore, it was not inactivated by the organisms which inactivate penicillin by the production of penicillinase, and which are so common as secondary factors in cases of gas gangrene.

(Slide) This is a chart showing the spectrum of bacitracin. You will see that it is effective against a large group of organisms, staphylococci, streptococci, pneumococci, gonococci, meningococci, diphtheria bacilli, and so on. It is not effective against many of the aerobic gram-negative rods, but it is effective against all of the gas gangrene clostridia and tetanus and also the anaerobic streptococci. These organisms are the ones that are to be considered as the essential causes of gas gangrene, with many secondary contaminants among the other bacterial groups. I wish to remind you also that bacitracin has significant synergistic action with penicillin in the inhibition of growth and the death of the gas gangrene organisms as well as other bacteria.

Some of you may remember that at the meeting of the American Surgical Association a year ago I reported on 105 cases of surgical infection treated systemically with bacitracin, and I brought up the fact that while we had found it effective in controlling many types of infection, we were beginning to run into cases which showed a considerable degree of kidney irritation. This was true particularly in cases treated in the spring of 1948, when we began to use material made by the deep tank growth of the organism, and which was inconsequential when we employed the earlier preparations made by surface growth.

We have now treated over 225 cases, and they can be divided into three groups. The first 75 patients were treated with the Ben Venue Laboratories product grown on surface culture and they showed very little evidence of nephrotoxicity. The next 75 patients were treated with the first product of the Commercial Solvents Company made in the deep

tanks, and some cases showed rather alarming albuminuria, and a rise in retained non-protein nitrogen, and in a few cases we were required to stop treatment for fear of serious kidney damage. The last 75 patients were treated with selected lots of the Commercial Solvents Company's product, and with these we have again had very little trouble. So that now we have regained our confidence in the safety of the systemic administration of this antibiotic although, for the present, it is wise to limit the dosage to 400 units every six hours per kilo of body weight.

After we had run into difficulties with the second group of cases, we took stock of our results and found that the toxicity was largely confined to certain lots. This is shown in the next slide.

(Slide) These are the lots made by the deep tank method. We had only one case of severe toxicity with the surface growth bacitracin. In that case, we had to stop treatment because of nausea and vomiting and albuminuria, but they promptly cleared up following cessation of treatment. However, with the deep tank lots, we made a careful study of the clinical evidences of kidney irritation. These results are divided into three groups—cases showing none or only slight and transient evidences, those with moderate but transient evidences, and those which we called severe because of nausea and vomiting or a degree of albuminuria, casts, or cells in the sediment, or a rise in N.P.N., which made us fear that the kidneys might be damaged. There were no fatalities, however, that could definitely be ascribed to bacitracin in any patients in this severe group. In this study we also noted those patients which had some evidence of kidney damage, probably due to the infection itself.

As a result of this study, since July 1, 1948, up to February 15, 1949, we have treated all of our cases except six with lots which have shown, by the Food and Drugs Administration test, an L.D. 50 of 500 units for a 20-Gm. mouse. The F.D.A. tests are shown on the slide, and have been correlated with the clinical results. You see here six cases treated with two lots which were more toxic according to that test, and these gave us a little

Degree of Toxicity According to Lot Numbers Used in the Systemic Administration of Bacitracin Prepared by the Deep Tank Method

Lot Number	F.D.A. LD 50–20 Gm. Mouse	Number of Cases*	Daily Dosage	Some Evidence of Kidney Damage Before Rx	Toxicity with Treatment		
					None or Slight Transient†	Moderate Transient‡	Disturbing§
January to June, 1948:							
C.S.471212S	287 ±18	19	40–260,000	9	2	8	9
C.S.471217S	255 ±20	5	88–260,000	2	0	4	1
C.S.471231S	240 ±21	8	40–280,000	3	1	5	2
C.S.480114S	283 ±18	15	40–196,000	6	5	8	2
C.S.480120S	361 ±23	14	14–200,000	4	9	4	1
C.S.480210S	262 ±17.7	10	16–160,000	3	2	2	6
C.S.480212S	224 ±15.2	7	50–188,000	5	0	2	5
C.S.480218S	500 or less	7	40–200,000	1	5	1	1
July, 1948, to February 15, 1949:							
C.S.480420	500	37	2–120,000	15	20	16	1
C.S.480408	500	9	40–80,000	5	6	3	0
C.S.480512	322 ±26.8	4	40–80,000	0	0	1	3
C.S.480520	435 ±80.9	2	10–40,000	0	0	1	1
C.S.480616	about 500	10	2–80,000	5	6	4	0

* A few cases were treated with more than one lot and are included with each lot used.

† Albumin one plus, occasional granular cast, a few white cells and epithelial cells.

‡ Albumin 2-3 plus, a few to moderate granular casts, white cells, epithelial cells. Treatment not interrupted.

§ Albumin 4 plus, moderate to many granular casts, white cells, epithelial cells and few to moderate red cells, or nausea and vomiting or significant rise in retained nitrogen. Considered advisable to stop treatment.

trouble. However, with five lots meeting this specification, the evidences of severe kidney irritation were minimal.

It is true that we have used somewhat smaller doses during this period also for fear of kidney irritation, but with the two lots of higher toxicity with which we got into difficulties, we used the same doses as with the less toxic lots and as soon as we stopped the former and treated these same cases with the latter lots, the difficulty disappeared. Therefore, with our experience with the last 75 cases we have developed an increasing confidence in the safety of this agent and if the manufacturers can meet this specification we believe that it can be more generally employed.

I do not wish anyone any hard luck, but I hope that I soon will have the opportunity of using bacitracin in the treatment of clinical gas gangrene. I shall use it in the next case I see, but I shall use it as an adjunct to surgery and antitoxin and such other methods of treatment as are indicated by the case in hand.

DR. WILLIAM R. SANDUSKY, Charlottesville, Va.: Dr. Meleney has just pointed out that the degree of toxicity among different commercial lots of bacitracin varies. Observations which we have made substantiate this point. We have used bacitracin in guinea pigs other than in the study just reported. In some it was administered in connection with experiments in which *Clostridium novyi* was the contaminating organism and in others bacitracin alone was given for the purpose of comparing two different commercial lots of the drug. Altogether bacitracin has been administered to 726 animals. Among this number there were 99 deaths due to causes other than clostridial infection. That drug toxicity is a possible cause of these deaths has already been discussed. The following table presents an analysis of these deaths in relation to varying dosages of two different commercial lots of the drug. It demonstrates that for the larger dosages there is a significant difference in the mortality rates between the two different commercial lots of bacitracin.

In closing, I should like to thank Dr. Lehman and Dr. Meleney for their comments on this work.

Analysis of Deaths from Causes Other Than Clostridial Infection in Relation to Total Dosage of Bacitracin

Bacitracin Units Per Gram	Lot B-471231S			Lot B-480420		
	Animals	Deaths	Mortality	Animals	Deaths	Mortality
30	91	57	63%	42	14	33%
15	..	..	..	42	0	0
10	85	13	15%	16	0	0
5	15	1	7%	10	0	0
4	..	..	..	9	0	0
3	..	..	..	336	8	2%
2	..	..	..	22	1	5%
1	..	..	..	33	3	9%
0.5	..	..	..	25	2	8%
	191	71	37%	535	28	0.5%

POSTOPERATIVE NITROGEN LOSS:*

A COMPARISON OF THE EFFECTS OF TRAUMA AND OF CALORIC READJUSTMENT

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OPERATION OR INJURY is generally accompanied by a serious deviation from the individual's customary habits of nutrition and activity. The effects of this change in routine must be considered before any conclusion can be drawn about physiologic alterations resulting from the actual trauma itself. Available information suggests that these factors have not been generally distinguished. Accordingly, when a surgical metabolism unit was established at the Presbyterian Hospital two years ago, one major objective was to provide information bearing on this problem of differentiating more clearly between the effects of operation and changes in routine. This paper presents the nitrogen balance data thus obtained under controlled conditions before and after surgery.

Negative nitrogen balance is considered to occur consistently after trauma to a previously healthy individual. The so-called "toxic destruction of protein," of earlier workers,[1-3] and the latter-day "catabolic" or "alarm" response attributed to activation of the adrenal cortex, are among the currently accepted hypotheses to explain this nitrogen loss.[4-9] "Anti-anabolism"[10] is an alternative concept to "catabolism," and postulates that exogenous, *i.e.* food, protein is completely wasted and excreted following injury, thus providing the excess nitrogen found in the urine. A reappraisal of these theories seems advisable in view of the results of the present study.

REVIEW OF PERTINENT LITERATURE

The demonstration that nitrogen is lost to the body in disease was established in the pioneer studies presented at the end of the last century and during the first two decades of this one. The greatest volume of work was done on patients with typhoid fever,[1, 2] but studies were conducted in erysipelas,[11] tuberculosis,[12] and other diseases[13, 14] as well. The inability of these early workers to prevent the sharp loss of nitrogen which occurred during the several diseases studied led to the theory that protein is destroyed as a result of toxins released during an infection. These toxins were considered as

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probably injuring cells or specific enzyme systems having to do with protein synthesis and retention. However, Shaffer and Coleman[1] demonstrated that diets with average amounts of protein, but with approximately 75 to 80 calories per Kg. of body weight, *i.e.* about 4000 calories, stopped the loss of nitrogen. They therefore concluded that no such phenomenon as toxic destruction of protein existed. Several years later, however, Coleman and DuBois[2] measured over brief periods the energy exchange of typhoid fever patients placed in the Russell Sage Calorimeter. From data so obtained they calculated the theoretical caloric requirement of these patients. Despite feeding this amount, nitrogen loss persisted. Accordingly, the workers readopted the "toxic destruction" concept to explain this persistent negative nitrogen balance. It should be noted, however, that their subjects lost weight on what was presumed to be an adequate caloric intake.

Twenty years later, Cuthbertson[4, 15] observed that fractures were accompanied by a loss of nitrogen to the body both in experimental animals and in man. This loss was greater than that accountable for through local tissue destruction. Cuthbertson was unable to overcome this reaction by increased feeding of protein, and described the phenomenon as a "catabolic response" to injury. In later experiments on rats, however, he[16] and Munroe and Cummings[17] observed that increased provision of protein and calories prevented all systemic loss of nitrogen, that is, loss in excess of that accounted for by local resorption from the injured area.

The war restimulated interest in the phenomena associated with trauma. The fact that increased provision of protein would not overcome the "catabolic response" to fracture was reaffirmed by Howard.[8] Negative nitrogen balance after surgical operations was noted by Brunschwig[18] and others. Meningitis[7] was found to cause nitrogen loss. In all these experiments the loss of nitrogen could not be overcome by increases in dietary intake. Albright,[6, 10] Browne[9, 19] and others postulated that the adrenal cortex was stimulated by injury, the so-called "alarm reaction" or "adaptation syndrome" of Selye.[5] As a result of this adrenal activity, either "catabolism" was produced with corresponding breakdown of tissue, or "antianabolism" took place, with inability to utilize incoming nitrogen for protein synthesis and tissue regeneration. These effects were felt to be mediated through the excessive secretion of a hypothetical "S" hormone of the adrenal gland.[6] Of interest was the fact that depleted subjects readily retained nitrogen upon forced feeding and showed no "alarm" response.

At about this time, contradictory reports began to appear in the literature. Several groups of workers found that the loss of nitrogen after operation or trauma could be prevented by increased dietary intake. Co Tui and workers[20] succeeded in this attempt with diets high in protein and calories, the former provided as a casein hydrolysate. Riegel and her associates[21] were able to define a minimal, although elevated, caloric and protein requirement at which nitrogen equilibrium could be assured after several types of operations.

Werner[22] also observed nitrogen equilibrium or marked sparing of expected nitrogen losses when he provided parenteral high protein, as amino acid solution, despite the concurrent administration of low calories. He observed nitrogen equilibrium as well in two patients with fractures and two with burns, excluding exudation and tissue destroyed, and given high caloric high protein regimens by mouth. Hirschfeld[23] overcame the expected urinary negative nitrogen balance in a large series of burn patients, although he questioned the wisdom of the extreme diets which were necessary.

The workers who were able to overcome the nitrogen loss after injury in non-depleted subjects, of necessity have denied that an abnormal mechanism exists consequent to injury. Peters[24] has written a critical review of the results obtained by this group, and concludes that proof is not yet at hand that incoming nitrogen can be utilized to prevent the losses consequent to injury in a previously healthy individual.

Werner[25] has pursued the subject from a different point of view. He studied the effects of the independent variation of calories and protein in healthy subjects in order to compare the extent of nitrogen loss with those following injury. He was able to demonstrate that such losses are readily sustained for several weeks and occur upon abrupt reduction in calories, or proteins, or both. These losses were comparable in degree to that seen after many operations or after injury. The present study is an extension of this work. In the experiments to be reported, the patient is made to serve as his own control. The same feeding program has been given after surgery as was provided before the procedure. The results have been contrasted to establish the added effects of trauma over those produced by changes in nutrition.

METHODS

All patients in this study were admitted to the Surgical Metabolism Unit of the Presbyterian Hospital, and customary methods for balance studies have been employed, as described elsewhere.[22, 26] Special nurses and dietitians were provided. A kitchen solely for the use of the unit was set aside. Weighed diets from stocks of food were served, and the nitrogen content of the diet and of the uneaten returns determined by a modified Kjehldahl procedure after homogenization in a Logeman homogenizer. Urine and stools were collected in 24 hour batches but were pooled in three or four day lots for determination of nitrogen content during periods of oral feeding. The determinations were done daily during intravenous nutrition in the postoperative period. Stools were pooled and determined once or twice during a dietary period through the study. Standard methods for the various chemical determinations which were used have been outlined elsewhere.[22, 26]

All patients were in good health and nutrition, and previously active. They were admitted for interval cholecystectomy or ventral or inguinal hernia repair done by the surgical resident staff, and were subjected to early ambu-

lation. Feeding was maintained during the day of operation as well as during standardized pre- and postoperative periods. Four groups of patients were studied (Groups I, II, IIIA and IIIB). Protein administration was maintained at a constant level throughout each experiment, but the level of calories was subject to change. Reduced caloric intakes were provided in order to insure the same constant intake after operation as before. The patients in Group I received a baseline diet by mouth of 30 to 40 calories (Kg. body weight) with 12.5 or 14.4 Gm. N per day for one week (Period I), then a reduced caloric intake of 18 to 24 calories per Kg. with unchanged N intake by mouth for one week (Periods II and III), then operation (Period IV) with provision for the next four days of the same caloric and nitrogen intake but parenterally administered* (Period V); finally a return for three days to the original baseline diet (Period VI). The patients in Group II were maintained as in Group I except that the second weekly period before operation was subdivided. Calories were reduced as in Group I except that they were given orally for four days (Period II), then parenterally* for the next three days just prior to operation (Period III). Similar parenteral administration was then continued after the procedure. The reason for this preoperative period of parenteral feeding was to document the effect of a shift in route of administration and in quality of the protein source. The patients in Group IIIA received a baseline diet for one week as in the first two groups, reduced calories parenterally as described in Group II for four days, baseline calories again for one week, then operation and four days on the same parenteral reduced calories as in the second period, and finally, a return to baseline nutrition. The patients in Group IIIB were maintained on the baseline diet with full calories described above for the first week before operation and for ten days thereafter.

RESULTS

A total of 26 patients were included in the study. There were ten men and 16 women. Ages ranged from 18 to 67. There were 11 patients undergoing cholecystectomy, six with ventral hernia repair, eight with inguinal hernia repair, (one bilateral), and one patient with a polyp removed from the colon by colotomy.

Group I.—Baseline; reduced calories by mouth; operation; and reduced calories parenterally. There were five patients in this group, three men and two women. The various feeding periods are outlined under the methods section. This group was the first studied and hence irregularities appear in the maintenance of constant nutrition in every instance. Three of the five patients in the group underwent hernia repair, one cholecystectomy, and one colotomy for a polyp of the colon. The average nitrogen balance for the

* Generous supplies were provided of a 10 per cent amino acid solution (VUJ-N) by Dr. A. Gibson of Merck & Co. and of a lyophilized amino acid material, Elamine, by the Interchemical Co., a division of American Cyanamide Corp.

various periods of the study is shown in Table I. On baseline intake of calories and nitrogen, the average N balance is +1.7 Gm. per 24 hours. On reduction of calories with constant N intake by mouth, the average N balance is −0.5 Gm. per 24 hours. The balance for the day of operation and the next four days on the same calories and N but given parenterally, as in the period before the procedure, is −3.6 Gm. per 24 hours, or a difference of −3.1 Gm. N per 24 hours from the preceding period (Table II). The average balance for the last period is −1.1 Gm. N per 24 hours.

TABLE I.—*Showing Average Daily N Balance in the Various Periods Before and After Operation: Patients Grouped According to Feeding Program.*

Patient Group	No. of Patients	Average N balance (Gm. N/24 Hrs.) Period I	Period II	Period III	Periods IV & V	Period VI
I	5	+1.7	−0.5	−0.5	−3.6	−1.1
II	12	±0.0	−1.9	−2.3	−2.4	−0.9
III B	6	+1.2	+0.5	−0.3	+0.7	−0.1
III A	3	+0.2	.....	−2.4	−4.2	−1.4

Group II.—Baseline, reduced calories by mouth, and unchanged low calories parenterally. There are 12 patients in this group, three men and nine women. All the men and four of the women underwent ventral hernia repair while five women were subjected to gall bladder removal. The details of the feeding program are summarized under the methods section. They are the same as Group I except that the period before operation is subdivided

TABLE II.—*Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation: Patients Grouped According to Feeding Program.*

Patient Group	Average N balance (Gm. N/24 Hrs.) Period III	Periods IV & V	N balance difference Period III—Periods IV & V
I*	−0.5	−3.6	−3.1
II	−2.3	−2.4	−0.1
III B	−0.3	+0.7	+1.0
III A	−2.4	−4.2	−1.8

*Group I inadequately maintained on nutritional schedule (see text).

so that the parenteral feeding given preoperatively (Period III) was duplicated postoperatively (Periods IV and V). The data for the various periods is summarized in Table I. It will be seen that the average daily N balance on parenteral low caloric feeding immediately before operation is −2.3 Gm. N while that of the day of operation and of the next four days on the same intravenous feeding is −2.4 Gm. There is a difference of −0.1 Gm. N per 24 hours (Table II).

Group IIIA.—Baseline; reduced calories parenterally; baseline; operation and reduced calories parenterally. There are three patients in this group, one

man and two women undergoing gall bladder excision. The results are summarized for each period in Table I. It is seen that the average daily N balance resulting from change to parenteral nutrition before operation is −2.4 Gms. while the same change in type of feeding after operation produces an average daily N balance of −4.2 Gm. There is a difference between the two periods of −1.8 Gm. N per 24 hours (Table II). It should be noted

TABLE III.—*Showing Average Daily N Balance in the Various Periods Before and After Operation in Patients Undergoing Cholecystectomy.*

Patient Group	Name	Average N Balance (Gm. N/24 Hrs.) Period I	Period II	Period III	Periods IV & V	Period VI
I	Wi.	+0.9	−0.4	−0.4	−4.4	+1.2
II	At.	+1.5	−1.2	−2.3	−2.4	−4.2
II	Be.	+1.7	−0.7	−2.4	−3.7	−1.3
II	Ro.	+0.2	−2.5	−0.8	−1.9	−0.7
II	Su.	±0.0	−1.4	−4.0	−2.4	+1.6
II	Ja.	+0.7	−1.9	−3.5	−2.8	−0.9
III B	Sa.	+2.9	+2.4	±0.0	−0.3	−1.7
III B	Ba.	+0.3	+0.9	−1.2	−2.4	−1.5
III A	Fe.	+0.8	.....	−2.7	−2.7	−0.3
III A	Qu.	+1.0	.....	−1.1	−3.4	−0.3
III A*	Ha.	−1.3	.....	−3.3	−6.6	−3.5
†Average		+0.8	−0.9	−2.1	−2.9	−1.0
Range		−1.3 to +2.9	−2.5 to +2.4	−3.5 to ±0.0	−6.6 to −0.3	−4.2 to +1.6

*Male.
†Average excludes cases in Group I unsatisfactorily treated (see text).

that one of the three patients had a high temperature following operation and another developed an undiagnosed complication postoperatively.

Group IIIB.—Baseline calories throughout. Six patients were maintained on relatively high baseline calories and protein throughout the experiment (Table I). Two were operated on for gall bladder removal, one for ventral hernia repair, and three for inguinal hernia repair. The average N balance

TABLE IV.—*Showing Average Daily N Balance in the Various Periods Before and After Operation: Patients Grouped According to Type of Operative Procedure.*

Type of Operation	No. of Patients	Average N Balance (Gm. N/24 Hrs.) Period I	Period II	Period III	Periods IV & V	Period VI
Gall-Bladder*.....	10	+0.8	−0.9	−2.1	−2.9	−1.0
Ventral Hernia.....	6	−0.2	−1.9	−2.1	−2.3	−0.8
Inguinal Hernia.....	8	+1.2	−0.4	−0.7	−1.0	−0.4
Partial Colectomy.....	1	−1.0	+1.4	+1.4	−0.6	−0.8

*One case in Group I excluded because of unsatisfactory maintenance of nutrition.

for each period is summarized in Table I. No significant change in nitrogen balance is seen following operation (Table II).

EFFECT OF OPERATIVE PROCEDURE

The cases in the above groups have been reclassified according to the type of operative procedure, without regard to nutritional schedule (Tables

III, IV, and V). A comparison of the isocaloric periods before and after operation reveals no significant difference in nitrogen balance between the pre- and postoperative periods of each of the surgical procedures studied. No significantly greater degree of negative balance is noted for one procedure over another (Table V). A daily balance difference average of −1.0 Gm. N is seen for the gall bladder subjects between the pre- and postoperative periods, of −0.2 Gm. N for the ventral hernia, and −0.3 Gm. N for the inguinal hernia patients. The results are even slightly better if the irregularly fed

TABLE V.—*Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation: Patients Grouped According to the Type of Operative Procedure.*

Type of Operation	Average N Balance (Gm. N/24 Hrs.)		N Balance Difference Period III—Periods IV & V
	Period III	Periods IV & V	
Gall-Bladder*.....	−2.1	−2.9	−0.8
Ventral Hernia.....	−2.1	−2.3	−0.2
Inguinal Hernia.....	−0.7	−1.0	−0.3

*One case in Group I excluded because of unsatisfactory maintenance of nutrition.

cases in Group I are excluded. Two of the ten gall bladder patients fed without interruption showed negative nitrogen balance increases of more than 1.5 Gm. N per day after operation.

EFFECT OF MAINTENANCE OF CONSTANT NUTRITION

The cases in the original groups have been regrouped according to the success with which constant isocaloric nutrition was maintained through the

TABLE VI.—*Showing Average Daily N Balance in the Isocaloric Periods Before and After Operation: Patients Grouped According to Success in Maintenance of Nutritional Schedule.*

Maintenance of Therapy	No. of Patients	Average N Balance (Gm. N/24 Hrs.)		N Balance Difference Period III—Periods IV & V
		Period III	Periods IV & V	
Poor.....	5	−0.5	−3.6	−3.1
Fair.....	6	−2.1	−2.8	−0.7
Complete.....	15	−1.5	−1.3	+0.2
Fair and Complete.....	21	−1.7	−1.7	±0.0

experiment. The results for the periods immediately before operation and following are summarized in Table VI. A significant increase in negative nitrogen balance following surgery is noted only in those patients in whom sharp irregularities in nutrition occurred — the "poor" classification. These latter show a difference in average daily nitrogen balance between the pre- and postoperative periods of −3.1 Gm. N as opposed to −0.7 Gm. N for the "fair" category and 0.2 Gm. N for the "complete success" group. The average daily difference in N balance after operation from before is ± 0.0 Gm. N for the combined "fair and complete success" groups.

EFFECT OF CHANGE FROM BASELINE TO LOW CALORIC FEEDING PREOPERATIVELY

Table VII shows the effect of a sudden change from relatively high levels of caloric intake, often insufficient to maintain body weight, to lower ones, *i.e.* from 30 to 40 calories per Kg. body weight to 18 calories per Kg. body weight. Protein intake was kept throughout. The same sharp negative nitrogen balance following caloric reduction occurs as has been reported elsewhere.[25]

TABLE VII.—*Showing Average Daily N Balance in the Periods of High and Low Caloric Feeding Prior to Operation.*

Patient Group	Average N Balance (Gm. N/24 Hrs.)		N Balance Difference Period I—Period II
	Period I	Period II	
I	+1.7	−0.5	−2.2
II	0.0	−1.9	−1.9
III A	+0.9	−1.9	−2.8

Table VIII demonstrates the average daily nitrogen balance which results upon change to intravenous from oral administration of a low caloric constant protein intake. No significant difference is found in the average for this group as a whole. However, five of the 12 patients show an increase in negative nitrogen balance of more than 1 Gm. N per 24 hours (−2.0, −1.9, −1.8, −1.3 and −1.1 Gm. N per 24 hours), as a result of shifting to intravenous administration.

TABLE VIII.—*Showing Average Daily N Balance in the Isocaloric Periods Before and During Intravenous Feeding Prior to Operation.*

Patient Group	No. of Patients	Average N Balance (Gm. N/24 Hrs.)		N Balance Difference Period II—Period III
		Period II	Period III	
II*	10	−1.9	−2.3	−0.4
III B*	2	+1.6	−0.6	−2.2
	Average	−1.3	−2.0	−0.7

*Does not include patients fed orally through Period III.

DISCUSSION AND CONCLUSION

Published studies concerning the extent and causation of body nitrogen losses which follow injury have not differentiated between the loss due to the actual trauma and that due to the inevitable changes in type of nutrition which accompany injury.[28] Such a distinction appears necessary in order to evaluate the effect of trauma, and may help explain why divergent opinions exist about the consequences of injury.

The present report concerns the results of a study in healthy patients undergoing cholecystectomy and ventral and inguinal hernia repair. It has been generally accepted that nitrogen loss follows these surgical procedures,

although there has been disagreement as to whether this loss can be overcome by dietary means in the case of the gall bladder operation. However, the data obtained in the current study reveal that no loss of nitrogen is found following a surgical procedure beyond that observed on the same caloric intake before the operation. This lack of response to the injury of operation is not explainable by previous depletion, since the patients were in good health, had lost no weight, and had had no recent infection. The failure of excesses of nitrogen to appear in the urine is difficult to harmonize with the concepts that abnormal mechanisms are invoked by trauma, namely, increased tissue destruction—"catabolism," or arrested utilization of exogenous, *i.e.* administered, nitrogen: "anti-anabolism."

Cholecystectomy, or hernia repair, may not be severe enough forms of injury to invoke these mechanisms, or may do so only occasionally. However, nitrogen loss has hitherto been regularly described after these operations[18, 29] when no increases in nutrition were provided. If this nitrogen loss is the result of inadequate nutrition, as appears to be the case, it becomes necessary to reexamine the reports concerning negative nitrogen balance following other operations and injuries in order to define the extent to which caloric deficits may have contributed to the total.

Such caloric deficits may be exaggerated by the additional caloric requirements resulting from fever. Furthermore, the estimation, and hence provision, of such needs is made difficult by inaccuracies in the measurement of heat production during constant fever and during periods of temperature change. Much information is available from the studies of patients with typhoid fever.[2]

The losses of nitrogen which occur during this latter disease were avoided by Shaffer and Coleman[1] by feeding high caloric regimens during the course of the disease. These workers denied the existence of abnormal mechanisms in the handling of nitrogen. Coleman and DuBois[2] revived the hypothesis of "toxic destruction" when they found persistence of negative nitrogen balance after feeding a theoretically adequate amount of calories as determined from calorimeter measurements. The weight loss of their patients indicates that their estimate of caloric need may have been faulty. Calculations based upon the concept that the law of conservation of energy pertains to these subjects indicates that an additional 1000 calories, or about 4000 calories total, might have maintained weight, and this is about the amount which prevented nitrogen loss in the work of Shaffer and Coleman. Apparent discrepancies from the law of conservation of energy exist[27] and it is possible that typhoid fever patients fall in a separate and intermediate category in terms of abnormal or "anti-anabolic" mechanisms produced by this disease as compared with operation and other types of infection.

A true "anti-anabolism" appears to follow recovery from scarlet fever and meningitis, according to Peters and his group.[7] Nitrogen is burned and excreted to the same extent as fed, by these subjects, despite elevated levels

of protein and caloric administration. This finding suggests the possibility that the presence or absence of infection may account for some of the discrepant results obtained by different workers attempting equilibrium following more severe injuries and operations than those reported in the present study. Infection not infrequently accompanies more radical surgery or trauma and may be masked for some time, whereas it was not a complication of the procedures reported here, except possibly in one instance. Should infection be the variable which is responsible for the appearance of abnormal mechanisms in the handling of nitrogen in some cases and not in others, it is of importance to recognize this in reporting on the effect of trauma. It is also necessary to take into account the effects of added caloric requirements resulting from such a complication. Otherwise mis-impressions may be gained about the consequences of injury by itself. Thus, the one male patient undergoing cholecystectomy had a moderate fever in the immediate postoperative period and a hidden covered infection which became manifest only later in the postoperative period. He does not therefore represent the nitrogen loss from uncomplicated operation.

Added support for the view opposing the existence of abnormal mechanisms consequent to injury uncomplicated by infection, is found in recent animal experiments.[30, 31] In the presence of a constant supply of adrenal cortical hormone given to adrenalectomized animals, loss of nitrogen occurs after injury exactly as in animals with intact adrenals. No increase in adrenal secretion is possible in the former animals, yet an "alarm" response is found. Thus activation of the adrenal cortex is ruled out as a mechanism to explain the negative nitrogen balance following injury, except as a functioning adrenal enables the body as a whole to react adequately.

In conclusion then, evidence is brought forward that certain operations are not accompanied by nitrogen loss beyond that produced by the same nutritional regimen provided before surgery. Lack of excessive nitrogen excretion is difficult to harmonize with the concept that abnormal mechanisms for the handling of protein have been invoked by the operations concerned. Interruption of nutrition, even if transient, produces nitrogen losses not compensated for by corresponding increases a day or so later. This is probably explained by the fact that nitrogen cannot be stored unless a definite minimum requirement of calories is also provided.[32] This minimum is greater than that generally furnished after operation, and is not attained by the slight increases in caloric intake mentioned immediately above. These losses should not be attributed to the effect of the trauma of operation. The role of infection has not been studied, and may well invoke responses not found following the operations reported here.

SUMMARY

1. Twenty-six healthy and non-depleted patients have been studied with the purpose of distinguishing the effect of the usual changes in dietary intake, postoperatively, from the effects of the trauma of operation *per se*.

2. Eleven patients in otherwise good health underwent cholecystectomy, six ventral hernia repair, eight inguinal hernia repair, and one colotomy.

3. The effect of shift from relatively adequate calories to the lower caloric intake usually given after operation has been studied preoperatively. This latter diet was then continued through the day of operation and beyond. Protein in the diet was kept constant. No significant increase in nitrogen output resulted from the operative procedure.

4. The implications of these findings have been discussed. The concept is proposed that simple caloric lack explains the postoperative nitrogen loss found following operation uncomplicated by infection.

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Discussion.—Dr. Champ Lyons: Our group at Tulane has been similarly interested in the problem of negative nitrogen balance following operative trauma. Unquestionably, restricted oral intake is responsible in considerable degree for the observed negativity of the balance. It occurred to us that it would be helpful to know whether or not protein made available by mouth or vein would be retained or rejected during the postoperative period of negative balance. Experiments were designed to study this simple problem without attempting to determine the ultimate utilization of retained nitrogenous substances within the body. Two types of experiments have been done.

Glycine synthesized to contain N_{15} has been fed as dietary supplement to healthy adults and the percentage of N_{15} excreted in the urine has been followed. The administration of adrenocorticotropic hormone (ACTH) to these subjects at the time of feeding tagged glycine has produced an increased total excretion of N_{15}. However, all of these subjects had previously had other studies with N_{15} and we cannot state that the ACTH effect was directed solely at the newly ingested N_{15}. It may ultimately be shown that some of the excreted N_{15} was mobilized from previously fed and retained nitrogen.

The expense of N_{15} has discouraged its extensive use. In order to continue these observations on a wider scale, the urinary clearance of intravenously injected amino acids, as suggested by Eckhardt and Davidson (J. Clin. Investigation, 27:727, 1948), were adapted to our purpose. Patients were placed on the metabolic division with nitrogen balance studies. Pre-operative and postoperative amino nitrogen clearances were performed. A series of normal subjects and surgical patients have been studied.

A typical experiment may be summarized as follows:

Slide 1. Two control periods of one hour each preceded the injection of Merck's VUJN mixture. The percentage of amino-N excreted in the urine during these control periods was negligible. The injection of amino acids required approximately 1 hour. Six per cent (6%) of the total amino N injected was excreted with the patient in N balance. This is a low figure, inasmuch as normal subjects may excrete up to 10 per cent of the total injected.

Slide 2. One day following radical mammectomy the patient was in negative nitrogen balance with reduced oral intake. A lag in the rate of urinary excretion is noted, but the quantity of amino-N excreted amounts to only 7.5 per cent of the total injected.

Slide 3. On the third postoperative day the nitrogen balance was still slightly negative. The rate of excretion was somewhat improved, but the total excreted was still 7.5 per cent.

Slide 4. On the eighth postoperative day the patient was ambulatory and eating well. The nitrogen balance was positive. The urinary excretion rate had returned to the preoperative pattern, and the total amino-N excreted was 8 per cent of that injected.

Conclusions. Although it seems likely that ACTH increases the rate of excretion of newly available protein substrates, we have been unable to demonstrate accelerated excretion of injected amino-N in postoperative patients in negative nitrogen balance.

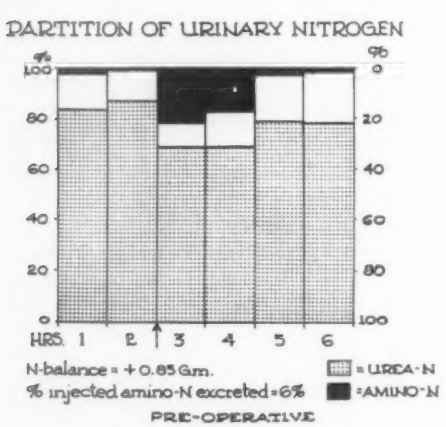
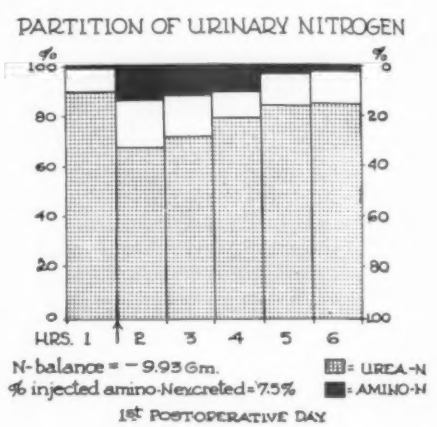


CHART I



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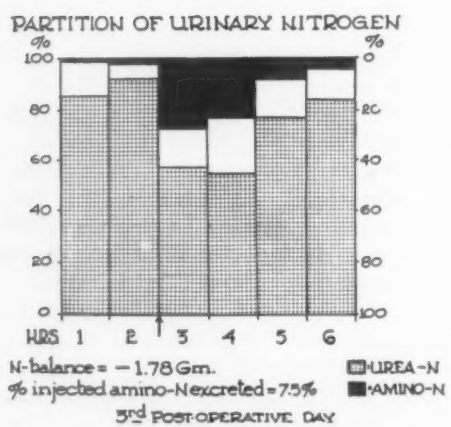

CHART III

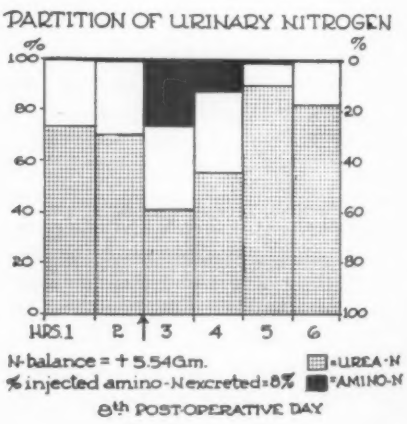

CHART IV

Dr. Oliver Cope, Boston, Mass.: Dr. Werner and his colleagues have rightly tried to differentiate the negative nitrogen balance due to starvation from that due to a possible theoretic, so-called alarm reaction of endocrine origin.

It is an enormous help to us to have internists like Dr. Werner, schooled in metabolic observation, to guide us through these problems. Dr. Werner has demonstrated that in operations of the type mentioned, and under conditions under which the operations are carried out, starvation accounts for what negative nitrogen balance there is.

On the other hand, I would like to point out that these patients were for a long time conditioned to the hospital prior to the operation. I was brought up by my older surgical teachers to realize that no patient was a better operative risk than an old patient with a gallbladder who had been in bed for a month prior to operation.

In contrast to Dr. Werner's results are the observations of Dr. John Howard at Johns Hopkins, who showed that the nitrogen balance, or metabolic reaction of the patient to operation and trauma, varied according to the size of the trauma, and also to the health of the patient. He showed that a patient with a traumatic compound fracture of the femur, who was well, healthy and vigorous before the accident, had an enormous so-called catabolic reaction, whereas in a patient who had been sick and was in a chronic debilitated state prior to the fracture, no such reaction occurred, and the patient had a nitrogen balance like that which Dr. Werner has described.

This is a knotty problem, hard to pick to pieces, and I am certain that it is by such careful studies as Dr. Werner has presented to us that eventually we will know the origin of the reaction to operation and how to meet it.

Dr. David V. Habif: Dr. Lockwood asked me to say a few words in regard to the paper. I should like to say first that the patients were selected only because they were healthy, without previous weight loss, and because they were willing to spend an extra two-week period pre-operatively on the surgical metabolism service to serve as their own control, as Dr. Werner has already mentioned.

All patients were operated on by the resident staff, so that they were not selected in the sense of having a fine or rapid operation by skilled attending surgeons.

The caloric intake decided upon was the amount that could be met parenterally both pre- and postoperatively. We have heard of the high concentrations of glucose given elsewhere without thromboses but these patients received only 7½ per cent glucose with at times alarming thromboses of arm veins. It would appear that the length of time the needle is in the vein is important, and the resulting thromboses are a limiting factor in this type of experiment.

Another complicating feature arose which was not appreciated beforehand in that in some patients there was a much greater loss of glucose in the urine postoperatively. Since quantitative urine glucose determinations were done both pre- and postoperatively, and the amounts administered intravenously were the same, it was found that up to 112 Gm. of glucose were lost postoperatively. Pre- and postoperative glucose tolerance tests have been found to be the same, so that at present we have no explanation, and the problem is under study.

We are all familiar with the fact that minor complications postoperatively do influence nitrogen balance, so that in such a study as has been presented it is important to judge the effect of operation alone and not operation plus perhaps an obscure minor complication.

Not only is it impossible with present-day facilities in many instances to give sufficient calories to prevent a negative nitrogen balance and weight loss following trauma or operation, but it appears impossible to quantitate the requirement. For example, working with Dr. John Nickerson of our Department of Physiology, we have studied the cardiac outputs of some of these patients with the ballistocardiograph which he designed. There appears to be a marked increase in cardiac output not suspected from clinical observation alone, and this work of the heart in itself would require a considerable number of calories. As

well, the B.M.R. done both before and after operation showed that there is more than the expected ten per cent rise per degree of fever in the immediate postoperative period.

This study was concerned chiefly with investigating the mechanisms involved in nitrogen loss following trauma, and if the conclusions are true, that the excess nitrogen loss is due to insufficient calories, it should be possible, in the long-term case, by providing such calories, to maintain positive nitrogen balance without weight loss. This is the aim of current studies.

Dr. Sidney C. Werner, New York, N. Y.: My lengthy preliminary remarks have resulted in my being unable to make some of the statements which I might have made to anticipate what Dr. Cope has justly brought up.

The question of whether more severe trauma can be compared with the lesser degree of trauma which follows gallbladder removal, ventral hernia repair, and so on, is naturally a cogent one. One would have to study each type of procedure in order to gain information which one would consider as proof. However, I do not think it unreasonable to suspect that if the body reacts to trauma in a given way for one degree of injury, that the reaction will be the same with more severe traumata.

One big factor in all such work is the control over the added caloric requirements of resultant fever. Hirschfeld, with large amounts of calories and protein, has been able to restore nitrogen equilibrium in burn patients, and in our own hands we were able to do the same. Moreover, in a patient with a burn or a compound fracture, there is the added factor of infection, which must be accounted for. Also, for the first few days, adequate feeding is not generally given, protein is drawn upon as a fuel, and so the body becomes adapted to a high rate of nitrogen turnover. This creates a lag in adjustment to diets with less nitrogen and nitrogen losses may persist for a week or so just on this account. In experiments with normal people given a high level of nitrogen intake, this outpouring of nitrogen will persist when the intake level is reduced to normal for some time after the change in diet. All of these influences have to be evaluated before the presence or absence of abnormal mechanisms can be established.

Dr. Lyons' discussion was very much to the point, and reminds me of several animal experiments which I mentioned earlier, by Noble and by Ingle, which indicate, also, no abnormal mechanisms follow injury. They found that following adrenalectomy in the experimental animal, the rat, if one gives adrenocortical extract in a constant amount before and after operation, one gets a typical alarm response and an outpouring of nitrogen, despite the fact that there is no possibility of the adrenal cortex suddenly secreting an excess of adrenocortical steroids. It would appear, therefore, that the function of the adrenal is to permit the body to react adequately to its needs following trauma, rather than that the adrenal is responsible for the nitrogen loss which follows trauma.

It should be stressed that this discussion of injury does not necessarily apply to the factor of infection which may be something else again.

MINIMUM POSTOPERATIVE MAINTENANCE REQUIREMENTS FOR PARENTERAL WATER, SODIUM, POTASSIUM, CHLORIDE AND GLUCOSE*

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UNDER NORMAL CONDITIONS of oral intake it is sometimes but not always easy to assure an adequate nutritional intake for the surgical patient. When the patient is unable to take anything by mouth and all intake must be parenteral, the responsibility of the surgeon increases; for while a definite measurable intake is more readily achieved, it is more difficult to know just how much of each element should be injected. Indeed, it is important to know just how little may be injected, i.e., the minimum needs to maintain normal function. Such knowledge is of practical value because it will avoid the inconvenience and expense of unnecessary, and the danger of excessive, injections. In order to study the probable minimum requirements, a series of observations were made on surgical patients given daily 2000 cc. of fluid containing glucose with and without added sodium chloride for four postoperative days. The findings suggest that a smaller intake of both water and salt than is usually given seems to be adequate. Moreover, specific data on potassium losses and glucose utilization were also obtained.

PREVIOUS WORK

The basis upon which surgeons estimate the water, electrolyte and glucose needs for the parenteral maintenance of the postoperative patient is, to a considerable extent, theoretical and traditional. In the early days of parenteral therapy large volumes were given, as much as four and five liters per day, not for the correction of deficits, but for maintenance of normal water balance. This was perhaps part of the then general belief in the value of a large fluid intake as illustrated by the still frequent order "force fluids." More significant than the large volumes injected was the fact that these fluids contained 9 Gm. of salt per liter because this was the only way in which isotonicity was achieved. Even when glucose was added later, the influence of tradition on the need for saline was not changed. Thus the amount of salt injected was often as great as 27 or even 36 Gm. per day, which is three to four times the intake of a normal individual. As might be expected, difficulties due to retention of fluid were produced though for a long time the casual connection was unrecognized. These difficulties were serious,

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and sometimes led directly to a fatal outcome. They arose because the human kidney could not excrete the large amount of salt, and therefore retained water with it to maintain the osmotic pressure of the body fluids. The clinical effects of this tremendous increase in body fluids were manifold —pulmonary edema, wound disruptions, peritonitis from failure of apposed peritoneal surfaces to heal, and circulatory impairment. So common did this danger become that Coller and associates[2] sounded an emphatic warning in 1944 in a report entitled *Postoperative Salt Intolerance.*

At the present time, most surgeons give the average adult postoperative patient unable to take anything by mouth 3000 cc. of water parenterally for maintenance alone, more to correct abnormal losses. Of this, one liter generally contains isotonic salt, so that the sodium chloride intake is nine Gm. a day, the amount an average normal individual is supposed to ingest in an average normal diet. Actually this may be much smaller, as indicated by analyses we have made on a number of patients on the usual hospital diets. As to glucose, the practice varies, some using 5 per cent glucose with or without amino acids, others a combination of 5 and 10 per cent glucose with or without amino acids. The intake of glucose and amino acids with three liters thus varies from 100 to a maximum of 300 Gm. of each.

Specific data on the minimum water, salt and glucose needs are rather limited. Cooper, Iob and Coller[3] have carried out carefully controlled studies of the urinary response for a period of only 30 hours after infusions of 5 per cent glucose in normal men and in patients following operations of varying magnitude. They observed a definite postoperative oliguria which was associated with a minimal output of sodium and chloride. Patients undergoing less severe operations, such as herniorrhaphy, as well as abdominoperineal resection, both experienced periods of low water output which later changed to diuresis. Sodium and chloride were excreted more rapidly during the periods of low water output, but were conserved during the diuresis stage. The average sodium loss was less (47.3 meq.) after abdominoperineal resection than after herniorrhaphy (107 meq.). Berry, Iob and Campbell,[1] in the same patients measured the potassium output in the first 30 hour postoperative period and found losses from 30 to 119 meq. The younger patients excreted more potassium than older ones undergoing the same operation, and those who had the more severe operative procedure, e.g., abdominoperineal resection, excreted on an average 73 per cent more free potassium than the controls who did not undergo any operation, or those subjected to herniorrhaphy. Howard[13] studied chronically ill surgical patients given an intravenous intake for six preoperative and six postoperative days. He found that on a constant intake of sodium and chloride (about 12 Gm. daily), despite considerable individual variations, most patients showed retention of salt after operation. He also found that on an intake of 50 meq. a day, more potassium was lost immediately after than before operation. The greatest loss occurred

during the second postoperative day. This agrees with the findings of Reifenstein[16] who studied a patient after spinal fusion. Reifenstein also found that urinary excretion of sugar or reducing substances was increased after operation. The type of anesthesia and duration of operation are not mentioned.

PROCEDURE AND METHODS

In order to study this problem of minimum water, salt and glucose needs, balances were measured in a series of patients. We adopted first of all a volume intake of 2 liters, basing this on theoretical considerations. In various groups glucose was given in two concentrations, 5 and 10 per cent; in the latter concentration one series contained no salt intake, in another the intake consisted of 9 Gm. a day.

In all, 40 surgical patients were studied. They were unselected except for the criteria that they must have no clinical evidence of cardiovascular or kidney disease. The operations performed varied, although most of them consisted of uncomplicated cholecystectomy. Their preparation for operation did not necessitate special regimens such as blood, chemotherapy, etc. The preoperative medication was morphine and atrophine. All anesthesia was induced with sodium pentothal followed by gas-oxygen-ether. Nearly all cases were studied for an arbitrary experimental period of four consecutive days or 96 postoperative hours. A few patients were also studied before operation. During this time all intake was by intravenous injection. Any patient with a source for abnormal postoperative fluid or electrolyte loss (i.e., vomiting, biliary or gastro-intestinal drainage exceeding 100 to 200 ml.) was eliminated. Urine was collected during 24 hour periods and measured; an aliquot was obtained and preserved with toluol and refrigeration. The electrolyte content of small amounts of emesis occurring during the first postoperative day was included in the first 24 hour specimen. Heparinized samples of blood were withdrawn before operation and at the end of the study. Specific gravity and pH of the urine were determined by hydrometer and by glass electrode respectively. The urines were analyzed for sodium and potassium by means of the Weichselbaum-Varney flame photometer;[20] for chlorides by the method of Harvey,[11] for total nitrogen by the macro-Kjeldahl method of Hiller, Plazin and Van Slyke,[12] for creatinine by the method of Folin[7] adapted for the spectrophotometer, for acetone by the Legal nitroprusside test, and for sugar by the method of Somogyi,[17] for inorganic phosphates by the method of Fiske and Subbarow.[6] The plasma was analyzed for sodium and potassium by means of the Weichselbaum-Varney flame photometer,[20] for chlorides by the method of Van Slyke and Hiller,[19] for N.P.N. by the method of Folin[7] adapted for the spectrophotometer, and for plasma proteins by the method of Weichselbaum.[21] Hematocrit measurements were done on heparinized blood in a Wintrobe tube.

Blood transfusions were given several patients following operations other than cholecystectomy. The amount of blood was estimated to replace that lost during operation. In calculating balances no allowance was made for the electrolyte content of this blood except for the sodium citrate it contained. None of the patients undergoing cholecystectomy required blood replacement and it is this group of patients which were studied in greatest detail. These were divided into three groups.

One group of patients undergoing uncomplicated cholecystectomy received daily infusions of 2 liters of 10 per cent glucose in water; a second group

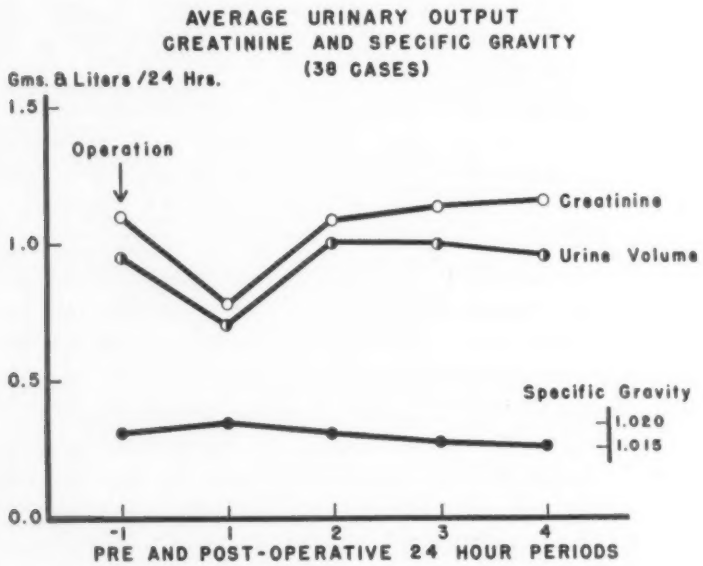

FIG. 1.—The graph represents the averages in 38 patients receiving an intake limited to 2 liters of intravenous glucose per day. Statistical analysis reveals that the changes from day to day were significant. Note the constancy of the specific gravity and the parallel fall in the creatinine content and urine volume in the first postoperative 24 hour period. Note also that after the first day the urinary output averaged one liter per day, which would be considered adequate.

received 2 liters of 10 per cent glucose in water to each of which 4½ Gm. of sodium chloride had been added; and a third group received 2 liters of 5 per cent glucose in water. Each patient's first infusion was started between 8 and 9 A.M., and his second between 4 and 5 P.M. The duration of each infusion was approximately three hours. There was no oral intake during the period of study. All patients were observed during the fall, winter and spring months.

FINDINGS

The findings are described under three headings: water, electrolyte and glucose.

Water.—The findings dealing with water balance are limited to measurements of urinary volume, creatinine, and specific gravity. Figure 1 shows the average daily pre- and postoperative values of 38 patients whose daily infusions consisted of 2 liters of 10 per cent glucose in water or 2 liters of 10 per cent glucose in water containing a total of 9 Gm. of NaCl. The addition of salt did not influence these findings. One notes that the daily urinary output approaches a liter per day except during the first 24 hour postoperative period. During this day the urinary output averages 750 ml. in comparison to 930 ml. for the day prior to operation, and 1000 ml. for the second and third postoperative days. These figures were subjected to careful statistical analysis and found to be significant in their day to day difference.

The oliguria noted during the first 24 hours after operation is accompanied by a fall in creatinine output, but without any change in specific gravity. Not every patient experienced this oliguria and the degree varied. The ages, which ranged from 19 to 75, did not seem to be a factor. The severity of the operation may be a factor but the number of various procedures studied was insufficient to draw definite inferences. Blood replacement at the time of operation in 12 cases did not seem to prevent oliguria during the first 24 postoperative hours. The operative records of these patients were examined and none had significant hypotension during their operations. In spite of the relatively normal urinary output, many of these patients experienced variable degrees of thirst which might indicate that the water intake was too low despite the adequate urinary output. However, there was no certain indication that this thirst was any different than it is in patients who received 3 liters of water. Controlled observations of this subjective symptom are difficult but perhaps deserve more study.

Electrolyte.—First of all are the observations on patients receiving no salt at all. These include 21 patients whose data are summarized in Table I. The operations were of various kinds, but the intake in all patients was limited to two liters of 10 per cent glucose intravenously a day. Scrutiny of these data reveals the fact that on no electrolyte intake and despite much individual variation, there is a conservation of salt as shown by a gradual decrease in the amount of sodium and chloride excreted on each consecutive day during the four day postoperative study period. Patients who received blood replacement on the day of operation tended to lose on an average slightly more sodium and chloride than those not needing blood replacement. In general, those receiving blood were the ones subjected to a more severe operation.

Age proved to be a factor in the individual variations in electrolyte conservation as shown by the data in the six cholecystectomized patients listed in Table I; three were young, aged 19, 27 and 28, and they excreted daily, over the 96 hour study period, an average of 7 meq. of Na and 17 meq. of chloride, in contrast to the older patients, aged 56, 59, and 64, who excreted twice as much, i.e., 20 and 34 meq. respectively. Thus, with no electrolyte

TABLE I.—*Postoperative Output in Urine Per 24 Hours*
Daily Intake 2000 cc. 10 Per Cent Glucose in Water

Case	Age Sex	Op.	Postoperative 24 Hour Periods																			Cumulative Loss			
			1					2					3					4								
			Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	N
1	19F	GB	28	45	37	24	3	19	14	30	13	6	13	13	13	7	4	2	7	13	11	6	62	79	93	18
2	56F	GB	.....					36	57	44	37	7	12	35	24	18	6	5	12	21	4	8	53	104	81	20
3	54F	GB	53	23	59	9	2	40	24	45	20	4	21	14	33	2	4	13	5	20	0	2	126	66	156	13
4	28F	GB	13	27	13	26	6	3	11	14	12	5	2	8	7	12	5	2	6	3	8	4	20	53	37	20
5	59F	GB	51	25	79	16	2	18	33	23	34	3	14	20	15	5	5	3	13	4	10	3	86	93	123	12
6	27F	GB	19	15	31	14	2	11	30	27	33	5	3	4	14	16	4	1	17	5	24	7	33	66	77	18
7	75F	GR*	32	18	29	15	4	30	23	24	17	8	52	44	40	35	11	.....					114	84	93	19
8	53F	GR*	40	21	40	26	5	81	28	17	28	8	33	50	65	38	22	31	29	40	8	14	184	128	162	49
9	72M	GR*	23	39	23	20	4	52	54	48	26	6	61	41	65	22	7	23	31	120	20	6	164	165	257	23
10	74M	JE	30	23	32	35	6	17	17	25	58	5	23	15	33	9	5	.....					70	54	89	16
11	58F	JE	5	2	12	1	3	6	2	12	1	2	7	2	10	5	2	2	8	33	12	6	20	14	63	13
12	59F	HY*	96	69	70	30	7	83	38	20	28	8	24	21	14	18	6	107	17	14	10	4	157	145	119	25
13	42F	HY*	19	36	42	3	4	15	37	34	5	7	7	19	19	10	6	5	14	17	15	8	44	106	111	25
14	41F	HY*	62	72	68	67	5	53	31	36	32	6	41	28	58	23	6	13	17	33	8	4	167	147	195	21
15	39F	HY	63	42	73	48	4	38	31	57	27	3	45	54	48	13	2	.....					146	127	179	8
16	39F	HY	42	38	27	8	3	8	38	23	6	8	8	10	22	33	11	8	20	15	43	10	66	105	87	32
17	37F	HY*	43	83	56	77	7	14	50	45	56	9	21	55	30	43	21	3	13	22	18	6	81	201	153	43
18	43F	RM*	60	75	62	67	7	37	66	83	49	8	16	30	41	18	8	22	38	59	36	11	144	209	245	34
19	40M	IH	18	13	26	12	3	30	42	53	37	10	9	51	47	38	10	7	24	29	38	10	64	129	157	32
20	31F	TH	101	112	91	99	11	10	17	23	49	4	11	16	14	35	4	11	14	18	24	4	134	157	146	23
21	32M	EL*	21	7	13	31	4	20	29	11	65	10	6	12	19	10	9	16	39	13	24	7	62	88	65	30

*Key: Same as in Table III.

intake, the younger patients seem able to conserve more Na and Cl than the older patients, when each is subjected to the same operation under similar conditions.

The pattern of electrolyte loss on no salt intake is shown graphically in Figure 2, which is based on the six cholecystectomized patients already mentioned. Although there were considerable individual variations, the average figures picture accurately the trend in all, i.e., the gradual fall in the amount of Na and Cl excreted, thus showing an efficient conserving

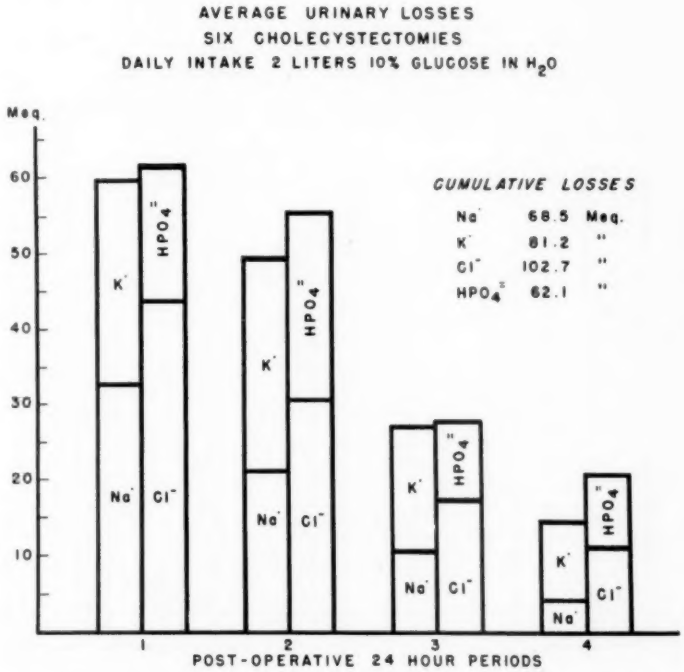

FIG. 2.—There was no salt intake in these patients. Note the decreasing output of sodium and chloride ion due to a conserving mechanism. Note, however, that the total average sodium loss during the 96 postoperative hours as sodium chloride was about 4 Gm. Note that the loss of potassium is more uniform and amounts, by the end of the 96 hour period, in terms of potassium chloride, to 6 Gm.

mechanism for these ions in the absence of any intake. On the other hand, potassium and phosphate tended to be excreted at a uniform rate during the first two 24 hour periods, and in some cases had a greater output during the second 24 hour period than during the first. The 96 hour cumulative loss was fairly small (Na 68 meq., K 81 meq., Cl 103 meq., HPO_4 62.1 meq., N. 16.9 Gm.) and represents about 4 Gm. calculated as NaCl and 6 Gm. calculated as KCl. It is not surprising, therefore, that this loss was accompanied by no significant changes in the blood levels of these electrolytes nor by any

alteration in the CO_2 combining power, serum protein or hematocrit. (Table IV)

In order to compare the salt loss before with that after operation, one patient (Fig. 3) was given glucose in water during two preoperative periods. The same decrease in output of Na and Cl was again seen. The operation *per se* did not seem to affect this pattern of salt conservation in that the progressive fall in excretion of Na and Cl continued. On the other hand, potassium and phosphate behaved differently, i.e., more was excreted postoperatively, especially in the second postoperative 24 hour period.

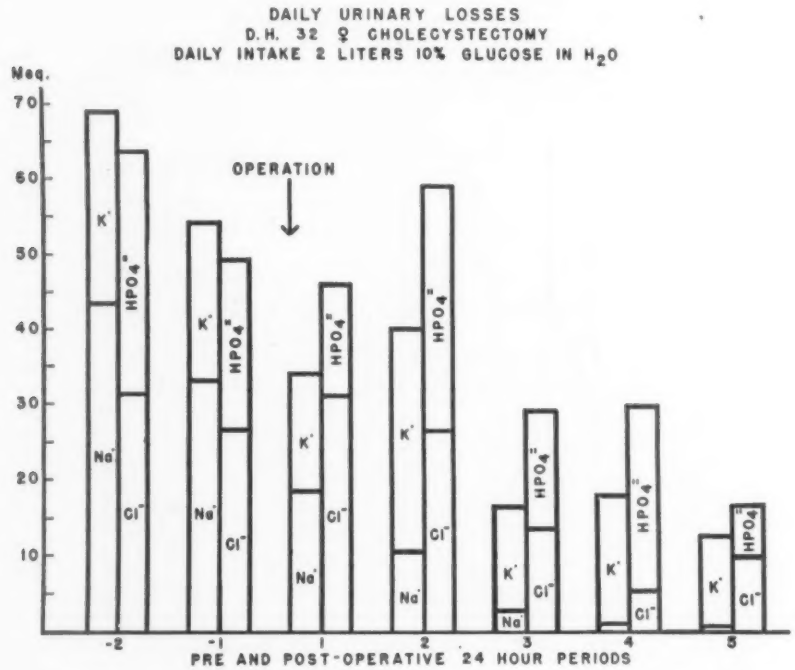

FIG. 3.—Pre- and postoperative urinary losses in electrolyte. This patient was given no salt before or after operation. Note that the pattern of conservation of sodium and chloride ion is not influenced by the operation. On the other hand, note the consistent and even increased loss of potassium and phosphate as influenced by operation.

In the next group of patients, the same regimen was carried out except for the addition of 9 Gm. of sodium chloride a day. Table II summarizes the urinary losses of 11 patients receiving daily intravenous infusions of 2 liters of 10 per cent glucose, each liter containing 4.5 Gm. of sodium chloride. The individual variations are great, but the findings show a pattern of retention of sodium and chloride similar in each patient. This is shown especially by the graphic representation (Fig. 4) in the five patients who underwent an uncomplicated cholecystectomy. For the first 24 hour postoperative period 76 per cent of the sodium injected and 70 per cent of the

TABLE II.—*Postoperative Output in Urine Per 24 Hours*
Daily Intake 2000 cc. 10 Per Cent Glucose in One Half Isotonic Saline

Case	Age Sex	Op.	Postoperative 24 Hour Periods																			Cumulative Balance			
			1					2					3					4								
			Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	N
1	51F	GB	33	25	39	18	2	146	94	150	100	9	134	10	132	18	7	90	6	89	27	4	+209	−134	+205	−22
2	59F	GB	21	8	20	32	4	39	14	33	21	7	190	13	157	12	7	131	8	90	9	9	+234	− 42	+318	−26
3	53F	GB	31	17	41	17	2	26	11	61	26	3	.....					.....					.....			
4	46F	GB	23	12	27	8	1	139	60	154	42	7	125	26	145	11	5	63	22	103	36	4	+266	−120	+185	−17
5	48F	CO*	50	27	53	39	3	94	42	185	13	9	151	32	154	6	7	131	27	167	6	5	+190	−128	+138	−24
6	58F	AP*	54	44	72	17	5	75	26	90	4	7	116	16	151	16	6	108	10	127	4	4	+362	− 97	+313	−23
7	71F	SR*	25	28	48	24	4	132	30	129	32	7	165	23	169	8	6	91	19	109	6	5	+139	−100	+ 84	−21
8	53F	TC	97	31	99	15	9	129	31	146	16	11	185	7	191	13	6	199	15	212	13	5	+ 6	− 83	− 34	−32
9	46F	EL*	102	52	160	38	6	56	25	68	27	4	139	21	153	14	4	170	18	169	....	4	+162	−116	+ 64	−18
10	71F	GR*	27	24	25	28	2	101	75	77	32	11	137	54	93	23	8	108	15	70	6	7	+207	−168	+351	−28
11	44F	GB	75	75	103	38	5	126	49	145	37	6	149	30	140	6	5	73	11	80	4	3	+192	−165	+149	−19

*Key: Same as in Table III.

chloride was retained. Of the total 9 Gm. of sodium infused during the first 24 hour period, this represents a retention of nearly 7 Gm. of NaCl. Retention of both Na and Cl continue during the second 24 hour period and during the third 24 hour period the excretion of sodium and chloride approaches the intake. The cumulative retention of Na and Cl for the 96 hour study period averages 39 per cent for Na and 37 per cent for Cl. This is equivalent to a retention of about 14 Gm. of the 36 Gm. of sodium chloride infused over the 96 hour period. The cumulative loss of K averaged 110.7 meq. and of HPO_4 98.5 meq.

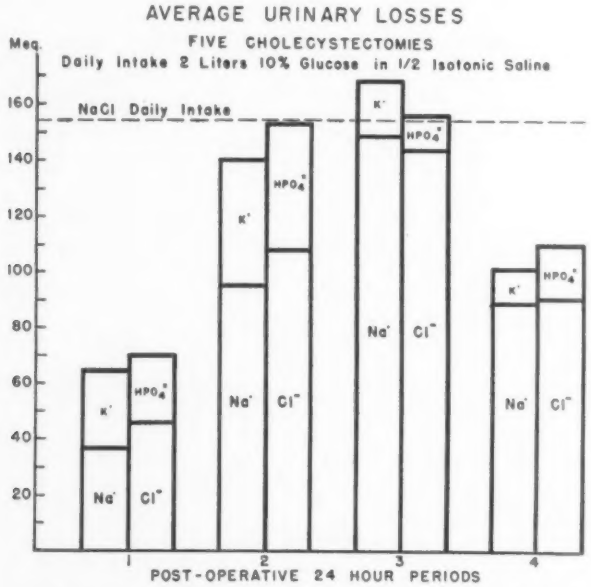

FIG. 4.—These patients received 9 Gm. of salt each day, equally divided between the 2 liters of 10 per cent glucose. Note the retention of sodium and chloride ion most marked on the first day and then decreasing. Calculation of the averages in this group showed that about 40 per cent of the injected sodium chloride was retained by the body. Note on the other hand the consistent losses of potassium and phosphate, which indeed were greater on the second than the first day.

In order to show the influence of preoperative intake, the data on one patient, a 42-year-old female who underwent an uncomplicated cholecystectomy is shown in Figure 5. She was given 2 liters of 10 per cent glucose and 9 Gm. of sodium chloride both before and after operation. This patient was ill prior to her admission to the hospital and had not been eating normally, but had not vomited. Note the retention of both Na and Cl preoperatively. This is similar, though even more marked in degree than the postoperative retention of sodium chloride of the patients in Figure 4. After operation, however, there was a retention of only 24 per cent of the Na and

TABLE III.—*Postoperative Output in Urine Per 24 Hours*
Daily Intake 2000 cc. 5 Per Cent Glucose in Water

Case	Age Sex	Op.	Postoperative 24 Hour Periods																			Cumulative Loss			
			1					2					3					4								
			Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	P	N	Na	K	Cl	N
1	36F	GB	10	8	13	6	1	37	43	77	31	5	3	21	32	14	4	6	10	14	16	3	55	82	135	13
2	64F	GB	28	25	74	22	2	49	96	55	9	11	8	23	23	4	7	1	5	20	11	7	86	149	170	27
3	46F	GB	21	45	46	40	5	26	37	65	30	8	12	19	27	12	5	5	13	15	15	6	63	112	152	25
4	23F	GB	3	28	13	34	7	1	14	0	44	5	.5	9	7	.....		.....					.....			
5	61F	EL	19	59	16	70	8	18	27	8	45	11	35	25	28	34	8	9	17	8	23	7	45	135	59	34
6	67F	AP*	9	5	15	34	5	7	25	21	26	8	6	15	32	23	7	.....					22	44	114	21
7	35M	EL	40	114	70	90	11	3	13	14	17	5	7	12	11	21	6	6	34	17	5	14	56	172	116	35
8	36F	GB	88	65	134	5	6	69	37	57	1	8	13	17	18	1	5	10	16	18	3	6	179	135	181	25

Key:

All values expressed as milliequivalents except nitrogen (N) which is expressed as grams.

*—Patients given blood at operation.
GB—Cholecystectomy.
GR—Gastric Resection.
JE—Jejunostomy.
HY—Hysterectomy.
RM—Radical Mastectomy.
IH—Incisional Herniotomy.
TH—Thyroidectomy.
EL—Exploratory Laparotomy.
CO—Colectomy.
AP—Abdominal Perineal Resection
SR—Sigmoid Resection.
TC—Transverse Colostomy.

4 per cent of the Cl infused during the first 24 hour period, which is much lower than average. The output of NaCl approached the intake during the third day. The cumulative retention at the end of seven days of study, during which the same intake was given each day entirely by vein, was 125 meq. of Na and 159 meq. of Cl. This is equivalent to a retention of roughly 12 per cent of the sodium and 15 per cent of the chloride, or in grams, a retention of only 7 to 9 Gm. of the 63 Gm. of NaCl infused during this period, much less than the average as previously noted.

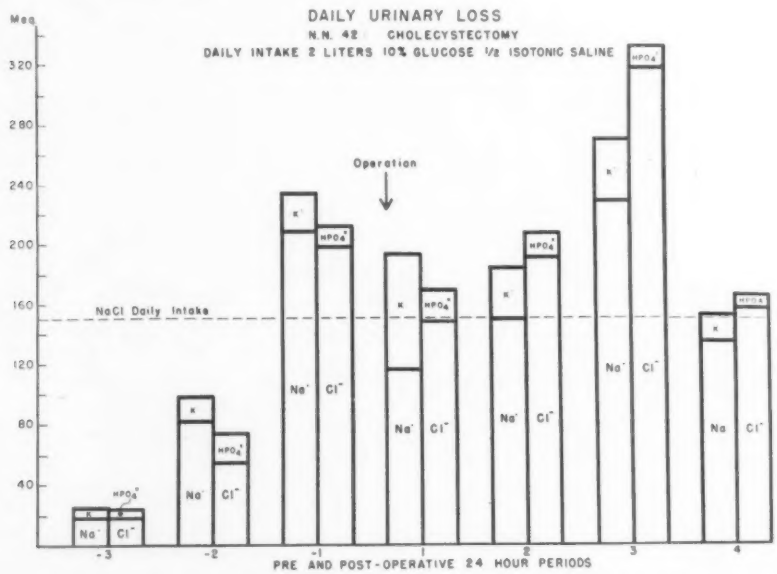

FIG. 5.—This patient received the same amount (9 Gm.) of NaCl both before and after operation. Note that there was an even greater degree of retention of sodium chloride before operation as compared with the findings in Figure 4, presumably due to the fact that the patient took very little but water before this preoperative period of observation. Note also that the degree of retention after operation was less pronounced than in the cases shown in Figure 4, thus illustrating the influence of previous salt intake.

The effect of a reduction in intake of glucose on electrolyte behavior is shown in Table III. This summarizes the electrolyte and nitrogen losses of eight patients receiving by daily intravenous injection 100 Gm. of glocuse, i.e., 2 liters of 5 per cent glucose in water. The 96 hour cumulative losses are fairly small (Na 88 meq., K 108 meq., Cl 144 meq., HPO_4 63 meq., and N 22.4 Gm.), but somewhat greater on an average than those patients receiving 200 Gm. of glucose. Moreover, these losses were similarly accompanied by no significant changes in the blood levels of these electrolytes nor by any significant alteration in the CO_2 combining power, serum proteins or hematocrit. (Table IV)

Glucose.—The findings in regard to glucose concern the observed differences between an intake of 100 Gm. and one of 200 Gm. First of all are the

TABLE IV.—*Pre- and Postoperative Blood Chemical Measurements*

			Pre-operative Blood									Post-operative Blood								
Pt	Operation	Intake/Liters	Cl	CO_2	Na	K	A	G	T	NPN	Hcrit	Cl	CO_2	Na	K	A	G	T	NPN	Hcrit
MC	Cholecystectomy.....	2.0 10% ½ISS	108.0	63.5	145.0	4.61	5.22	2.68	7.90	15	43.8	99.5	65.5	142.5	4.30	5.50	3.05	8.20	17	42.4
DR	Cholecystectomy.....	2.0 10% ½ISS	92.0	....	137.0	2.55	4.50	3.00	7.50	..	42.8	100.5	75.5	146.7	3.00	3.86	3.29	7.15	28	38.8
FL	Cholecystectomy.....	2.0 10% ½ISS	114.6	57.8	140.0	4.30	4.95	2.85	7.80	17	42.6	118.0	65.8	137.5	3.38	4.17	2.78	6.95	16	36.9
EP	Cholecystectomy.....	2.0 10% ½ISS	116.0	64.0	148.5	3.78	4.78	2.42	7.20	19	48.0	.....	63.1	150.0	3.65	3.70	2.60	6.30	17	42.0
LR	Ileo-Sigmoidostomy.....	2.0 10% ½ISS	102.5	61.1	140.5	3.72	5.49	3.21	8.70	12	44.4	120.0	70.6	.....	....	3.90	2.65	6.55	21	30.2
AF	Abd. Peri. Res.....	2.0 10% ½ISS	107.5	63.3	142.0	4.00	5.85	3.95	9.80	21	44.3	108.0	62.9	141.3	3.70	5.23	3.37	8.60	16	39.5
LA	Res. Primary Anast.....	2.0 10% ½ISS	111.0	70.0	135.0	4.80	4.49	3.66	8.15	21	44.0	106.0	....	140.6	4.56	3.57	3.82	7.40	..	38.0
EG	Trans. Colostomy.....	2.0 10% ½ISS	116.0	69.9	145.0	3.67	4.56	2.19	6.75	29	44.0	110.0	74.0	139.0	3.26	3.90	2.75	6.65	21	44.0
FH	Gastrotomy, Exp. Lap....	2.0 10% ½ISS	118.0	60.7	146.0	4.40	4.35	2.45	6.80	25	44.0	114.0	74.7	147.1	3.66	3.86	2.04	5.90	13	39.0
CM	Subtotal Gastrectomy....	2.0 10% ½ISS	110.0	71.3	140.5	4.95	3.19	2.19	5.38	31	41.0	117.0	....	.....	....	3.46	2.54	6.00	....	36.0
NN	Cholecystectomy.....	2.0 10% ½ISS	123.0	57.8	151.0	3.36	4.64	2.76	7.40	13	38.0	116.0	72.6	146.0	3.59	4.21	2.64	6.85	12	39.0
MS	Colectomy, Trans.....	2.0 10% ½ISS	120.0	65.0	144.0	3.59	4.56	3.14	7.60	14	43.0	117.0	72.4	154.9	3.36	3.84	2.71	6.55	23	41.7
PB	Cholecystectomy.....	2.0 10% ½ISS	88.0	61.5	138.9	4.04	5.17	2.08	7.25	17	36.0	121.0	71.7	148.0	3.96	4.17	2.68	2.85	14	39.0
MG	Cholecystectomy.....	2.0 10% HOH	111.0	59.0	145.0	6.00	5.10	1.90	7.00	15	41.0	106.0	55.6	141.0	5.05	4.60	2.30	6.9	20	37.6
MG	Cholecystectomy.....	2.0 10% HOH	.....	....	.....	....	....	....	....	..	....	105.0	68.1	142.0	4.60	4.40	3.10	7.5	25	39.8
FH	Cholecystectomy.....	2.0 10% HOH	.....	....	.....	....	....	....	....	..	....	105.0	60.8	147.5	4.20	4.40	2.90	7.3	..	....
EH	Cholecystectomy.....	2.0 10% HOH	102.5	....	142.0	5.50	4.60	3.20	7.80	..	44.0	99.0	57.6	134.0	4.20	4.30	3.50	7.8	42	44.0
DH	Cholecystectomy.....	2.0 10% HOH	.....	....	.....	....	....	....	....	..	....	97.0	62.1	135.0	4.10	4.30	3.00	7.3	12	41.0
MT	Gastric Resection.....	2.0 10% HOH	104.3	51.9	140.5	4.73	4.47	3.53	8.00	31	48.6	88.0	56.7	131.0	4.55	4.41	3.69	8.1	31	47.7
CV	Gastric Resection.....	2.0 10% HOH	108.0	16.1	145.0	5.90	5.90	3.50	9.40	25	44.5	98.0	69.5	135.1	6.01	4.48	3.62	8.1	25	25.7
WP	Gastric Resection.....	2.0 10% HOH	110.7	60.6	137.3	5.62	4.86	2.09	6.95	32	37.0	98.0	....	136.2	5.00	4.16	2.99	7.15	..	40.0
MC	Abd. Pan Hysterectomy..	2.0 10% HOH	103.0	69.8	134.0	4.23	4.95	4.25	9.20	18	40.9	95.0	76.7	.....	....	4.67	4.53	9.2	20	....
FW	Abd. Hysterectomy.....	2.0 10% HOH	104.0	61.6	136.8	4.24	5.24	3.26	8.50	15	34.0	98.5	66.6	137.5	3.70	5.60	3.10	8.7	18	33.0
DO	Hysterectomy.....	2.0 10% HOH	106.5	66.9	132.4	4.25	3.68	7.67	6.35	19	40.0	96.5	65.0	.....	. ..	5.10	3.25	8.35	20	43.3
NH	Abd. Pan Hysterectomy..	2.0 10% HOH	101.5	66 0	140.2	4.24	5.16	3.84	9.00	21	34.4	98.5	60.6	133.0	4.00	4.95	2.75	9.7	24	31.2
MP	Abd. Hysterectomy.....	2.0 10% HOH	102.5	28.8	138.0	4.53	5.23	3.47	8.70	17	37.6	97.5	59.5	132.2	3.85	5.72	3.38	9.1	20	31.6
RD	Hysterectomy.....	2.0 10% HOH	107.5	58.5	136.5	5.30	4.94	3.66	8.60	17	34.9	101.5	65.4	142.0	4.13	4.48	3.52	8.0	..	....
KR	Inc. Hernia Repair.....	2.0 10% HOH	110.0	60.5	145.0	6.72	5.85	2.75	8.60	18	48.0	106.0	61.9	136.2	5.90	5.34	2.76	8.1	22	48.9
HH	Thyroidectomy.....	2.0 10% HOH	106.2	55.7	143.7	5.60	4.68	2.42	7.10	14	48.0	106.0	55.0	144.0	5.68	4.90	3.60	8.5	17	46.0
BB	Exp. Laparotomy.....	2.0 10% HOH	100.5	64.4	145.0	6.93	4.10	1.90	6.00	24	30.0	101.0	55.0	138.5	5.10	4.80	2.40	7.2	24	38.8

All patients received 10% glucose in water (HOH) or in half strength isotonic saline (½ ISS).
Key: All measurements of Cl, CO_2, Na and K were made in plasma and expressed as meq/liter.
A, G, T refer to Albumin, Globulin and Total Proteins in Plasma, expressed in Gm. per cent.
NPN refers to nonprotein nitrogen of plasma as mg%.
Hcrit is the hematocrit value expressed as a percentage of the whole blood volume.

nitrogen losses. These were surprisingly low in both groups. (Tables I, II and III.) On an average, but 20 to 25 Gm. of nitrogen were lost during the entire four day postoperative period or about 4 to 5 Gm. a day. Only two specimens contain more than 20 Gm., one on the third day following a gastric resection, the other on the third day following hysterectomy. Only 17 specimens of the nearly 160 examined contained 10 Gm. or more of nitrogen. Moreover, comparison of the nitrogen loss in patients receiving 100 with those receiving 200 Gm. of glucose reveal little difference, i.e., 26 as compared with 23 Gm. for the average total 96 hours. Scrutiny of the individual cases also reveals no significant difference.

In all three groups, glycosuria and acetonuria were observed (See Table V). Of eight patients receiving daily intravenous infusions of 2 liters

TABLE V.—*Glycosuria and Acetonuria Following Operation Daily Intake 2000 cc. per 24 Hours*

	I 5% Glucose (100 Gm.) in Water	II 10% Glucose (200 Gm.) in Water	III 10% Glucose (200 Gm.) in ½ Isotonic Saline
Number patients studied	8	10	11
Patients showing glucosuria	6	10	11
Average amount glucose spilled (Gms.)	12.9	18.4	34.1
Range in amount glucose spilled (Gms.)	2.2—24.3	1.5—88.0	6.1—82.8
Av. rate of infused glucose in Gms./kg. body wt./hr.	.23	.48	.52
Patients showing acetonuria	6	2	6
Number 24 hour urine collections examined	31	37	39
24 hour urine collections containing acetone (%)	52	5	21
24 hour urine collections containing glucose (%)	42	86	92
Av. cumulative 96 hour urinary Na loss (meq.)	72	87	(197)*
Av. cumulative 96 hour urinary K loss (meq.)	118	103	115
Av. cumulative 96 hour urinary Cl loss (meq.)	132	126	(177)*
Av. cumulative 96 hour urinary P loss (meq.)	1.82	1.27	1.28
Av. cumulative 96 hour urinary N loss (Gms.)	26	29	23

*This figure represents positive balance, i.e., retention of the injected sodium chloride in this group.

of 5 per cent glucose and water for four postoperative 24 hour periods, six had glycosuria at some time during this period and 42 per cent of the 24 hour urine specimens contained glucose. The average amount was 13 Gm. The range in degree of glycosuria varied from as little as 2.2 Gm. of sugar to 24.3 Gm. It should be emphasized, however, that the average rate of infusion was 0.23 Gm. per Kg. of body weight per hour. As to acetonuria, six of these eight patients showed a positive test at some time during their postoperative period and 52 per cent of the 24 hour urine specimens contained from traces to 4 plus acetone. Five of the six patients having acetonuria also showed glycosuria during the same 24 hour period on one or more occasions during the four days of study.

Of the patients receiving daily infusions of 2 liters of 10 per cent glucose and water, 10 with and 11 without added electrolyte, all had glycosuria and

86 and 92 per cent of the 24 hour urine specimens contained glucose respectively. The average amount spilled was 18 and 34 Gm. respectively, and the range varied from 1.5 to 88 Gm. of glucose. It should be emphasized that the average rate of infusion was 0.48 and 0.54 Gm. per Kg. of body weight per hour, or twice that of those receiving 5 per cent glucose. Only eight of the 21 patients had acetonuria varying from traces to 2 plus; all eight patients at one time or another had acetonuria and glycosuria during the same 24 hour period. Only minor differences were discernible between those receiving 10 per cent glucose in water and those receiving 10 per cent glucose in saline.

DISCUSSION

The objective regarding minimum needs suggested in the title of this report has only been partly met by the evidence herein presented. Nevertheless, a few inferences may be drawn as to how little the postoperative patient may be given to maintain normal function. It should be mentioned at the outset however that such inferences are based upon the assumption that balance studies are valid as a guide to estimating such needs. This assumption has the sanction of general acceptance. Moreover, it is logical to believe that in the absence of deficits, intake of each element should balance the output just as energy intake equalizes energy expenditure. One of the possible pitfalls is the statement "in the absence of deficits," the truth of which may be difficult to establish in each individual patient. Another pitfall is the possibility that even in the absence of deficits some elements may be retained with physiological improvement, or that, vice versa, a "negative balance" may be beneficial because the body wishes to rid itself of an excess of a normal biochemical constituent. In spite of these and perhaps other objections, inferences will be based upon the validity of the idea that a balance of intake and output indicates an optimum physiological state.

The data on water balance seem to indicate that in the normally hydrated adult 2 liters is an adequate fluid intake in the absence of pathological losses. This is shown by the fact that this intake was accompanied by an adequate urinary output. Body weights, it is true, were not determined, and this would have given accurate confirmation as to the amount of insensible water losses. However, the average difference between intake and urinary output was about one liter, which is roughly that of the insensible loss. Thus it is likely that the fall in body weight would have been approximately one Kg. per day plus whatever loss was due to an inadequate caloric or nitrogen intake. Thirst might be considered as a guide to the measure of water needs. As already mentioned, however, so many postoperative and post-traumatic patients experience thirst, even on a larger water intake, that its significance remains unestablished. The fact that blood studies showed no change in electrolyte concentration or hematocrit would seem to indicate that dehydration did not occur on this intake. Thus it would seem justified to infer that 2 liters are all that are necessary to maintain water balance in

the postoperative patient. This agrees rather well with data obtained on normal humans subjected to starvation.[8, 10, 24]

The oliguria observed on the first postoperative day was not unexpected since it is a common clinical observation that patients seldom excrete as much urine during this period as they do later. Of greater interest was the fall in the creatinine output with no change in specific gravity. Since creatinine is cleared by the kidneys so readily, and concentrating function is performed by the tubules, it would seem that the oliguria was due to a decrease in the effective renal plasma flow and filtration fraction. Further observations, however, are necessary to be sure that this was the correct explanation.

The electrolyte needs may be partially estimated from the findings herein recorded. It is true that the loss during an intake of water and glucose alone was not very great, and was accompanied by no fall in the electrolyte composition of the blood. However, even small losses are probably not without some significance. It would be a simple matter indeed to provide this intake by the addition of a few grams of sodium and potassium salts. On the other hand, the addition of 9 Gm. of sodium chloride seems too great inasmuch as there was a retention averaging about 40 per cent of that injected. The degree of retention is certainly greatly influenced by the previous intake, i.e., the lower the intake before operation the greater the degree of retention. This is due to a fairly well known lag in the ability of the human kidney to excrete salt above the previous level of intake. This is true under normal conditions of oral intake as shown by White and Findley,[22] and is especially true after operation as shown by Stewart and Rourke[18] and others. Whether operative or accidental trauma and anesthesia increase this lag cannot be inferred from the present data. Further studies with careful comparison of pre- and postoperative retention is needed. In any case, it would seem, on the basis of the present observations with a daily intake of 9 Gm. of NaCl, that 4 Gm. would probably not lead to retention. On the basis of the much smaller sodium chloride losses on no intake, a balance may be struck, indicating that an average of between 2 and 4 Gm. of sodium chloride a day would probably produce balance in the average patient. The need for adding potassium rests on the assumption that losses in this element should be replaced. On such a basis about one to 2 Gm. of potassium salt should be added to the daily intake. If both salts were added as the chloride, a much larger amount of chloride would be present than seems to be needed on the basis of the present findings. Cations can readily be added without anions in the form of sodium or potassium lactate or gluconate. This does not take into account other electrolytes such as magnesium and perhaps the anions sulfate and phosphate. Further observations will be needed before their requirements can be definitely established.

It must be admitted, of course, that for short periods of time it is unlikely that serious physiological impairment will follow small deficits in these electrolytes, such as might follow their deprivation. Thus it might be

argued that simple fluids without salt might be adopted as routine. The difficulty with this point of view is that one never knows when the parenteral route may be required for longer than a few days. Furthermore, exact replacement, while not always essential, is a better basis for therapy than conclusions drawn from the results of experience alone. Further observations are being made in order to determine more accurately what pattern of electrolyte intake will lead to balance under normal conditions.

Findings in regard to glucose needs may be discussed in two parts. First is its sparing effect on tissue protein breakdown. As will be noted, the tissue protein loss as measured by the nitrogen excretion in the urine was surprisingly low in all of the cases studied, indicating that in these instances at least there was very little catabolic reaction, a finding which is contrary to many we have previously made and which have been made by others.[4, 5] It is, therefore, not surprising that there was very little difference in the nitrogen loss when the glucose intake was 200 Gm. as compared with 100 Gm. This would seem to confirm the finding of Gamble[10] that in normal human beings an intake of 100 Gm. of glucose a day produces the maximum sparing effect on tissue protein breakdown, and that an increase to 200 Gm. does not decrease the tissue protein loss. It should be mentioned, however, that in the present observations a variable amount of glucose was lost in the urine, and that this loss was greater in those receiving 200 Gm. Thus the effective amount of glucose available for metabolic needs was much less than 200 Gm. and indeed in one case, was only about a little over 100 Gm. It seems unlikely, however, that even with full utilization of the entire 200 Gm. further reduction in the low nitrogen loss could be effected.

The second finding concerns the degree of glycosuria and acetonuria observed. Glycosuria and acetonuria were noted in a large percentage of the cases studied. Since the rate of injection even with the 10 per cent solution was fairly low, i.e., 0.52 Gm. per Kg. per hour, the appearance of glycosuria must be taken as an indication that the postoperative patient operated under gas-oxygen-ether anesthesia under the present circumstances cannot utilize glucose as well as the normal.[14] Even when the rate was half this, i.e., 0.25 Gm. per Kg. per hour, as was the case with the 5 per cent solution, sugar was still spilled in the urine. It is probable that this glycosuria might have been avoided if the injection had been started at a slower rate in accordance with the Staub effect, as reported by Pareira and Somogyi.[15]

Acetone in the urine occurred more frequently when 5 per cent glucose was given than when 10 per cent glucose was injected. Pareira and Somogyi[15] observed ketonuria in a postoperative patient during the injection of 5 per cent glucose, which disappeared with a change to 10 per cent glucose. We have no data as to the exact significance of this finding inasmuch as 24 hour urine specimens only were measured. The appearance of a small amount of acetone during even one or two hours of the total 24 hour period, while of

little significance, would give a positive result. Nevertheless, it must be admitted that even a small amount of acetone in the urine under these conditions means that at some interval of time during the 24 hours the liver was probably free of glycogen, or that ketone bodies were being produced more rapidly than they could be utilized.

From the findings herein presented and from other considerations, it would seem safe to conclude that a full caloric quota by the injection of 4 liters of 10 per cent glucose is not ordinarily necessary nor indeed desirable. First it would probably not spare any more tissue protein, and in fact merely would spare the breakdown of tissue fat. Moreover, it is unlikely that, without special control of the rate of injection, all of this amount could be utilized by the body after operation, but that much of it would appear in the urine. Finally, the mechanical problem of administering this much glucose would seem too great to be justified. Nevertheless, the appearance of acetonuria on the lower intakes deserves careful scrutiny. The claim of Pareira and Somogyi[15] that up to 350 Gm. spaced over the entire 24 hour period is needed to avoid ketosis suggests the need for further study of this question.

Glucose utilization is, of course, influenced by many factors, and it is probable that the use of gas-oxygen-ether anesthesia plays an important role. For example, it is likely that the same operative procedures carried out under spinal anesthesia might provoke much less glycosuria and acetonuria. The mechanism of these disturbances in carbohydrate metabolism as herein observed deserves further investigation.

The significance of the potassium losses may be discussed in terms of protein losses. This is usually done by establishing a K/N ratio based upon computing the potassium loss in millimols and the nitrogen loss in grams. This has been calculated in 26 of the patients observed in this study. Only six of them showed a value below three, and in most of them the figure was between four and six. A ratio of three or less is considered by most authorities to represent the normal relationship of intracellular potassium to protein. Our findings, therefore, suggest that the destruction of the patient's protoplasm was not the sole source of the potassium loss, and that much of it originated in another way, perhaps by loss of cell potassium without loss of protoplasm.

SUMMARY

1. Balance studies were carried out in 40 surgical patients on a completely intravenous intake for 96 postoperative hours, and in a few cases during several preoperative days. Study of the urinary output included volume, specific gravity, creatinine, sodium, potassium, chloride, phosphate, nitrogen, glucose and acetone. Blood levels of sodium and potassium chloride, CO_2, plasma protein and red cell volume were also measured before and after each study.

2. With an intake limited to 2 liters a day there was an adequate urinary output during the four postoperative days of about one liter except for a moderate oliguria during the first postoperative day. The oliguria was accompanied by a decreased creatinine excretion with no change in specific gravity.

3. With no electrolyte intake, the body rapidly conserves sodium and chloride, but not potassium and phosphate. The cumulative loss during four postoperative days averaged about 4 Gm. calculated as sodium chloride and 6 Gm. calculated as potassium chloride. No changes in plasma levels of sodium, potassium, CO_2, proteins or in red cell volume were observed on this intake.

4. With an intake of 9 Gm. of sodium chloride a day, there was a definite lag in excretion so that of the 36 Gm. injected, an average of about 14 Gm. was retained. The loss of potassium, however, was the same.

5. It is estimated from these findings that an intake of 2 liters of water plus 2 to 4 Gm. of a mixture of sodium and potassium chloride (or gluconate) would meet the minimum requirements for these elements in the postoperative patient.

6. Calculation of the potassium-nitrogen excretion ratio suggests that only part of the potassium loss originated from the breakdown of tissue protoplasm.

7. The nitrogen sparing effect of 200 Gm. of glucose was not significantly greater than 100 Gm. of glucose. On the other hand, because of an undoubted disturbance in carbohydrate metabolism, acetonuria was more frequent under the latter than under the former intake. Glycosuria conversely was greater with a 200 Gm. intake as compared with a 100 Gm. intake. In order to determine the minimum requirements for glucose, further observations will be necessary, particularly with regard to the influence of the rate of injection.

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DISCUSSION.—DR. ROBERT ELMAN, St. Louis, Mo.: In spite of the published warnings of Dr. Coller and many others, it has been my observation that too much intravenous fluid is still being given in many hospitals. I would include in this plasma and whole blood transfusions.

Not only are many of these injections costly and inconvenient, but are too often actually or potentially dangerous. Whenever we use this method of therapy, we therefore have the responsibility of knowing exactly the specific amounts of each element needed for maintaining normal physiological activity.

It was largely for this reason that we are making this preliminary report of the minimum parenteral requirements in patients who for one reason or another take nothing by mouth. I might say that the 96-hour period of observation we used was purely experimental. I don't want to leave the impression that all of our gallbladder patients required parenteral injections during such a long period.

Our objective could be expressed by a very simple dictum, that is, the use of better but less parenteral fluids.

On the basis of the present findings we believe that 2 liters of water and perhaps even a little less in the normal hydrated adult will meet these minimum requirements for water under conditions of the present study.

As to salt intake, we have confirmed the observations of Dr. Lester White, our professor of physiology, and others, that the normal human kidney lags in its excretion for several days whenever presented with salt above the previous level of intake. Since surgical patients often are on simple liquids before operation—and I am excluding those with salt losses due to vomiting, and so on—it is clear that their kidneys may not be able to excrete much salt, so that more will be retained than those on a normal intake up to 9 Gm. a day.

This behavior of the human kidney is quite unlike that of the dog, which excretes added loads of salt rapidly. This difference is one reason among others for the pitfalls which may come from translating data on animals to human beings.

Finally, I would like to point out that our findings on the disturbed utilization of sugar after operation, while perhaps not surprising, may be decisively influenced by the addition of amino acids, a factor which we are now studying separately. This is based upon a few observations made already, which indicate that the addition of amino acids to intravenous glucose in normal humans, at least, seems to increase the utilization of glucose by the tissues.

THE METABOLIC FATE OF THE INFUSED ERYTHROCYTE*

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INTRODUCTION

IN RECENT YEARS, there has been considerable interest in the nutritional problems of surgical patients. In particular, nitrogen metabolism has been extensively studied, and it has become increasingly apparent that most seriously ill patients require amounts of nitrogen far above the needs of normal individuals. Most of these same patients receive many blood transfusions, and the question arises "To what extent do these transfusions contribute to the patients' nutritional requirements?" In particular, should the infused red cell nitrogen, which quantitatively is two to three times greater than the associated plasma nitrogen, be included as intake in day to day balance studies?

At present no consistent policy has been adopted in this regard, some investigators[1-3] including the red cell nitrogen as intake, others not.[4] Where such nitrogen has been included in calculations of daily balance, apparent positive nitrogen balance has been readily attained, and the catabolic phase following injury has apparently been reversed. Other workers, in studies of similar patients, in which, however, the red cell nitrogen was not counted as a source of available nitrogen in the calculation of daily balances, were unable to reverse the negative nitrogen balance following injury. Clearly, such conflicting descriptions of results from similar studies indicate a clouded notion of the exact role played in the body metabolism by the infused erythrocyte. Actually, there has been relatively little quantitative data available on which to base a considered opinion. To clarify this situation, the present study was undertaken.

METHODS

Two adult, male medical students, healthy and ambulant, were boarded on the metabolic ward at the University of Illinois Research and Educational Hospital. They were each maintained throughout the period of nitrogen balance study on a five-day rotating dietary schedule. The diets were composed of natural foodstuffs and amounted to 0.75 Gm. protein and 45 calories per Kg. body weight daily. Fluid intake was not restricted. Activities, although not restricted to any absolute schedule, were relatively constant from day to

* Read before the American Surgical Association, St. Louis, Mo., April 22, 1940. The opinions expressed in this paper do not necessarily represent the official views of any governmental agency.

day. Body weights were recorded daily. Following a control period of about one month, fresh, separated red cells (drawn from male donors on the day of infusion),† resuspended in isotonic saline just before administration, were injected into each of the two subjects for two and three days, respectively. The subjects were group O, Rh-, MN. Group O, Rh- red cells were infused, and one transfusion in each series was made up of N cells. It was, therefore, possible to differentiate between the recipient and representative donor cells, and to quantitate, by the Ashby technic as modified by Ebert and Emerson,[5] the percentage of each cell type circulating.

Plasma volumes were measured by the T-1824 dye technic.[6] Total blood volumes and corrected circulating red cell masses were calculated from the observed dye plasma volumes and the venous hematocrits, applying the 0.85 correction suggested by Gibson *et al.*[7]

Red and white blood cell counts, hemoglobins, hematocrits, and reticulocytes were determined by routine methods.[8]

Nitrogen content of the food was calculated from standard tables,[9] corroborated by spot, full-day analyses of each diet used. Total nitrogen of food, infused cells, serum, urine and feces was determined by Ma and Zuazaga's[10] modification of the micro-Kjeldahl method of Keys. Urine was collected in two day periods; feces over five days (marked with carmine).

Serum NPN was measured by the method of Koch and McMeekin as modified by Daly.[11] Howe's method[12] was used for the estimations of albumin and globulin. Fecal urobilinogen was measured by the method of Terwen as modified by Watson.[13] The following liver function tests were performed: bromsulfalein,[14] thymol turbidity and flocculation,[15] serum bilirubin, direct and total.[16]

After the nitrogen balance studies were completed, the subjects were on diets of their own choice. Determinations of plasma volume, red cell masses, and routine hematology were carried out at various intervals until complete disappearance of the infused cells.

RESULTS

A. *Body Weight, Nitrogen Balance and Circulating Plasma Protein.* The data in regard to diet, body weight, nitrogen balance and circulating plasma protein are presented in Tables I, II, III, IV, and V, and Figs. 1 and 2.

Each subject was on a fixed dietary intake of 0.75 Gm. protein and 45 calories per day. This amounted to 8.1 Gm. of nitrogen and 3020 calories for the first subject (MNL 1) and 8.8 Gm. of nitrogen and 3315 calories for the second (MNL 2). Approximately 44 per cent of the calories came from protein. There was minimal variation among the five serially rotated diets.

On this regimen, body weights were maintained, and nitrogen excretions, both fecal and urinary, were essentially constant during the control periods (Tables II, III and Fig. 1). One subject (MNL 2) was in minimal positive

† Prepared by The Michael Reese Serum Center.

nitrogen balance of 0.1 Gm. per day, while the other (MNL 1) was in slightly more positive balance, 0.5 Gm. nitrogen per day.

After 26 and 18 days respectively, fresh, separated red cells were infused. Subject MNL 1 received approximately 225 cc. cells daily for three days; subject MNL 2, approximately 250 cc. daily for two days. In terms of red cell nitrogen, this amounted to a total of approximately 36 and 26 Gm. respectively.

TABLE I.—*Mean Daily Dietary Intake*

Nutrient	Subject MNL 1	Subject MNL 2
Calories	3020	3315
Nitrogen (Gm.)	8.1	8.8
Carbohydrate (Gm.)	330	365
Fat (Gm.)	165	180

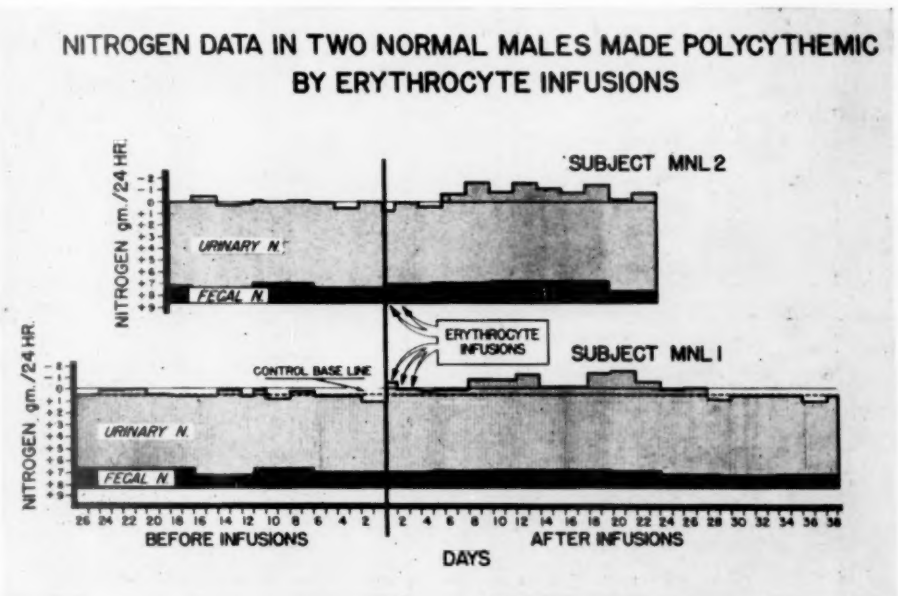

FIG. 1.—A slow steady excretion of "extra" nitrogen, over and above the preinfusion mean, follows the infusion of erythrocytes into normal males in amounts sufficient to produce a significant polycythemia. In the figure the nitrogen of the infused red cells is not charted as intake.

Thus, on the days of infusions, the total nitrogen intake of each subject was more than doubled.

Both subjects developed fever, malaise and the other evidences of an acute influenzal infection within 48 hours following the first red cell infusion. This persisted for two to three days, the highest temperature reached being about 102 degrees in each case. Neither subject was seriously ill. There was no evidence of any transfusion reactions.

TABLE II.—*Nitrogen Balance Data in a Normal Male Made Polycythemic by Erythrocyte Infusions*

Subject MNL 1—Nitrogen Intake 8.06 Gm. Daily

Day of Study	Weight (Kg.)	Urine Nitrogen (Gm.)	Fecal Nitrogen (Gm.)	Total Nitrogen Excretion (Gm.)	Nitrogen Balance (Gm.)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm./day)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm. cumulative)
Before Infusion							
26	66.9	6.28	1.31	7.59	0.47	....	....
25	67.0	6.28	1.31	7.59	0.47	....	....
24	66.6	6.60	1.31	7.91	0.15	....	....
23	66.4	6.60	1.31	7.91	0.15	....	....
22	66.5	6.65	1.31	7.96	0.10	....	....
21	66.7	6.65	1.34	7.99	0.07	....	....
20	66.7	6.29	1.34	7.63	0.43	....	....
19	66.6	6.29	1.34	7.63	0.43	....	....
18	66.7	6.15	1.34	7.49	0.57	....	....
17	66.6	6.15	1.34	7.49	0.57	....	....
16	66.3	6.59	0.86	7.45	0.61	....	....
15	66.5	6.59	0.86	7.45	0.61	....	....
14	66.5	7.10	0.86	7.96	0.10	....	....
13	66.5	7.10	0.86	7.96	0.10	....	....
12	66.3	6.55	0.86	7.41	0.65	....	....
11	66.4	6.55	1.38	7.93	0.13	....	....
10	66.7	5.90	1.38	7.28	0.78	....	....
9	66.0	5.90	1.38	7.28	0.78	....	....
8	65.9	6.51	1.38	7.89	0.17	....	....
7	66.5	6.51	1.38	7.89	0.17	....	....
6	66.5	6.39	0.86	7.25	0.81	....	....
5	66.2	6.39	0.86	7.25	0.81	....	....
4	66.0	6.39	0.86	7.25	0.81	....	....
3	66.1	6.39	0.86	7.25	0.81	....	....
2	66.4	7.00	0.86	7.86	0.20	....	....
1	66.4	7.00	0.86	7.86	0.20	....	....
After Infusion							
1	66.4	7.48	1.09	8.57	−0.51	1.01	1.01
2	66.8	6.97	1.09	8.06	0.00	0.50	1.51
3	66.9	6.97	1.09	8.06	0.00	0.50	2.01
4	66.3	6.78	1.09	7.87	0.19	0.31	2.32
5	65.9	6.78	1.15	7.93	0.13	0.37	2.69
6	66.6	6.78	1.15	7.93	0.13	0.37	3.06
7	66.4	6.78	1.15	7.93	0.13	0.37	3.43
8	66.5	7.73	1.15	8.88	−0.82	1.32	4.75
9	67.2	7.73	1.15	8.88	−0.82	1.32	6.07
10	66.7	7.64	1.25	8.89	−0.83	1.33	7.40
11	66.7	7.64	1.25	8.89	−0.83	1.33	8.73
12	66.8	8.06	1.25	9.31	−1.25	1.75	10.48
13	66.5	8.06	1.25	9.31	−1.25	1.75	12.23
14	66.5	7.02	1.25	8.27	−0.21	0.71	12.94
15	66.5	7.02	1.31	8.33	−0.27	0.75	13.69
16	66.4	7.04	1.31	8.35	−0.29	0.77	14.46
17	66.5	7.04	1.31	8.35	−0.29	0.77	15.23
18	66.0	8.21	1.31	9.52	−1.46	1.96	17.19
19	66.4	8.21	1.31	9.52	−1.46	1.96	19.15
20	66.6	8.49	1.27	9.76	−1.70	2.20	21.35
21	65.9	8.49	1.27	9.76	−1.70	2.20	23.55
22	66.4	7.53	1.27	8.80	−0.74	1.24	24.79
23	66.2	7.53	1.27	8.80	−0.74	1.24	26.03
24	66.4	7.09	1.11	8.20	−0.14	0.64	26.67
25	65.8	7.09	1.11	8.20	−0.14	0.64	27.31
26	66.0	7.37	1.11	8.48	−0.42	0.92	28.23
27	65.8	7.37	1.11	8.48	−0.42	0.92	29.15
28	65.5	6.30	1.11	7.41	0.65	−0.15	29.00
29	66.0	6.30	1.07	7.37	0.69	−0.19	28.81
30	66.0	6.61	1.07	7.68	0.38	0.12	28.93
31	65.6	6.61	1.07	7.68	0.38	0.12	29.05
32	65.9	6.68	1.07	7.75	0.31	0.19	29.24
33	65.8	6.68	1.07	7.75	0.31	0.19	29.43
34	65.5	6.61	1.12	7.73	0.33	0.17	29.60
35	65.5	6.61	1.12	7.73	0.33	0.17	29.77
36	65.6	6.31	1.12	7.43	0.63	−0.13	29.64
37	65.6	6.31	1.12	7.43	0.63	−0.13	29.51
38	65.5	6.70	1.12	7.82	0.24	0.26	29.77

TABLE III.—*Nitrogen Balance Data in a Normal Male Made Polycythemic by Erythrocyte Infusions*

Subject MNL 2—Nitrogen Intake 8.77 Gm. Daily

Day of Study	Weight (Kg.)	Urine Nitrogen (Gm.)	Fecal Nitrogen (Gm.)	Total Nitrogen Excretion (Gm.)	Nitrogen Balance (Gm.)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm./day)	Extra Nitrogen Excretion Above Preinfusion Mean (Gm. cumulative)
Before Infusion							
18	72.6	7.11	1.61	8.72	0.05	....	....
17	72.0	7.11	1.61	8.72	0.05	....	....
16	71.6	7.83	1.51	9.34	−0.57	....	....
15	71.2	7.83	1.51	9.34	−0.57	....	....
14	70.7	7.06	1.51	8.57	0.20	....	....
13	70.7	7.06	1.51	8.57	0.20	....	....
12	71.2	7.10	1.51	8.61	0.16	....	....
11	70.7	7.10	1.75	8.85	−0.08	....	....
10	70.2	6.92	1.75	8.67	0.11	....	....
9	70.3	6.92	1.75	8.67	0.11	....	....
8	70.5	7.00	1.75	8.75	0.02	....	....
7	70.7	7.00	1.75	8.75	0.02	....	....
6	70.7	7.30	1.30	8.60	0.17	....	....
5	70.4	7.30	1.30	8.60	0.17	....	....
4	70.0	6.82	1.30	8.12	0.65	....	....
3	70.1	6.82	1.30	8.12	0.65	....	....
2	70.3	7.34	1.30	8.64	0.13	....	....
1	69.9	7.34	1.30	8.64	0.13	....	....
After Infusion							
1	70.2	6.24	1.61	7.85	0.92	....	....
2	71.0	7.01	1.61	8.62	0.15	....	....
3	72.0	7.01	1.61	8.62	0.15	....	....
4	71.7	6.62	1.61	8.23	0.54	....	....
5	71.2	6.62	1.64	8.26	0.51	....	....
6	71.0	7.76	1.64	9.40	−0.63	0.73	0.73
7	70.0	7.76	1.64	9.40	−0.63	0.73	1.46
8	70.5	8.67	1.64	10.31	−1.54	1.64	3.07
9	70.4	8.67	1.64	10.31	−1.54	1.64	4.70
10	69.7	7.68	1.75	9.43	−0.66	0.76	5.45
11	69.8	7.68	1.75	9.43	−0.66	0.76	6.20
12	69.9	8.46	1.75	10.21	−1.44	1.54	7.73
13	69.7	8.46	1.75	10.21	−1.44	1.54	9.26
14	69.3	7.92	1.75	9.67	−0.90	1.00	10.25
15	69.6	7.92	1.75	9.67	−0.90	1.00	11.24
16	69.4	7.62	1.75	9.37	−0.60	0.70	11.93
17	69.9	7.62	1.75	9.37	−0.60	0.70	12.62
18	69.7	8.25	1.75	10.00	−1.23	1.33	13.94
19	69.4	8.25	1.75	10.00	−1.23	1.33	15.26
20	68.9	7.79	1.01	8.80	−0.03	0.13	15.38
21	69.2	7.79	1.01	8.80	−0.03	0.13	15.50
22	69.8	8.29	1.01	9.30	−0.53	0.63	16.12
23	70.1	8.29	1.01	9.30	−0.53	0.63	16.74

Beginning at once after the infusions in subject MNL 1, and after a few days in subject MNL 2, "extra" nitrogen, 0.5 to 1.0 Gm. daily over and above the preinjection control mean values, appeared in the urine (Tables II and III and Fig. 1). Fecal nitrogen was unchanged. The increased urinary nitrogen excretion persisted throughout the period of observation (23 days post-infusion) in subject MNL 2. Subject MNL 1 was followed for a longer period of time, and the "extra" urinary nitrogen excretion lasted for about one month. Thereafter, nitrogen excretion became stabilized at the preinjection level.

TABLE IV.—*Nitrogen Excretion in Normal Males Made Polycythemic by Erythrocyte Infusions*

(Extra-nitrogen Excretion Above Pre-infusion Mean, cumulative, expressed as per cent of infused erythrocyte nitrogen)

Day of Study After Infusions	Subject MNL 1	MNL 2
1	2.8	0
2	4.2	0
3	5.6	0
4	6.4	0
5	7.5	0
6	8.5	2.8
7	9.5	5.6
8	13	12
9	17	18
10	21	21
11	24	24
12	29	30
13	34	36
14	36	40
15	38	43
16	40	46
17	42	48
18	48	57
19	53	59
20	59	60
21	66	61
22	69	62
23	73	64
24	74	....
25	76	....
26	78	....
27	81	. .

In Fig. 2 and Table IV the "extra" urinary nitrogen, expressed as per cent of the infused red cell nitrogen, is listed cumulatively. It is apparent that although the subjects received different quantities of red cells, and excreted different absolute amounts of excess nitrogen, the excretion was proportionately the same. By the time the preinjection urinary nitrogen level was reached, "extra" nitrogen *mathematically equivalent to* (*but not necessarily derived from*) 80 per cent of the infused red cell nitrogen had been excreted.

The total circulating plasma proteins (Table V) remained essentially unchanged throughout the control and experimental periods.

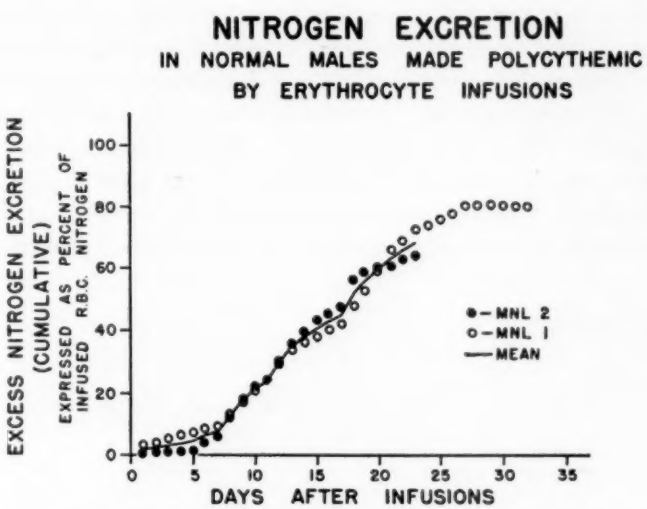

FIG. 2.—It is apparent that the quantities of "extra" nitrogen excreted following erythrocyte infusions in normal males is proportional to the quantity of red cell nitrogen infused.

TABLE V.—*Total Serum Protein, Albumin and Globulin in Normal Males Made Polycythemic by Erythrocyte Infusions*

Day of Study	Total Protein (Gm./100 ml. serum)	Albumin (Gm./100 ml. serum)	Globulin (Gm./100 ml. serum)	Total Circulating Serum Protein (Gm.)	Total Circulating Serum Albumin (Gm.)	Total Circulating Globulin (Gm.)
Subject MNL 1						
Before Infusion						
17	6.5	4.4	2.1	190	130	61
6	6.6	4.5	2.1	195	130	60
After Infusion						
8	6.1	4.1	2.0	...	...	..
16	6.6	3.9	2.7	190	110	77
22	6.6	4.7	1.9	185	130	53
51	6.2	4.4	1.8	190	135	55
87	5.9	4.1	1.8	190	130	58
108	6.7	4.4	2.3	...	...	..
Subject MNL 2						
Before Infusion						
6	6.3	4.2	2.7	225	150	96
3	6.0	3.9	2.1	215	140	75
After Infusion						
8	6.3	3.7	2.6	225	130	93
16	6.1	4.1	2.0	...	...	..
22	6.3	4.1	2.2	230	150	80
48	6.1	4.1	2.0	235	160	78
86	6.2	4.2	2.3	225	155	85
107	6.1	4.2	1.9	215	150	68

B. *Plasma Volume, Red Cell Mass, Erythrocyte Survival and Production.* In order to follow erythrocyte survival, serologically identifiable red cells had been infused. It was therefore possible to differentiate between representative donor and recipient cells, and to quantitate the number of each cell type circulating.

In Fig. 3 and Table VI plasma volumes, red cell masses, and survival of the donor and recipient cells in subject MNL 1 are plotted. There were no significant changes in plasma volume throughout the period of study. Following the infusions, there was a progressive fall in the initially increased red cell

TABLE VI.—*Plasma Volumes, Hematocrits and Red Cell Masses in Normal Males Made Polycythemic by Infusions of Erythrocytes*

Day of Study	Plasma Volume (ml.)	Hematocrit %	Total Red Cell Mass (ml.)	Subject's Own Red Cell Mass (ml.)	Infused Red Cell Mass (ml.)
Subject MNL 1					
Before Infusion					
17	2860	43	1800	1800	0
6	2985	42	1820	1820	0
After Infusion					
3	2930	..	2485	1810	675
16	2860	51	2535	1960	575
22	2780	47	2175	1625	550
38	3195	40	1810	1310	500
51	3070	41	1800	1430	370
87	3205	40	1835	1725	110
Subject MNL 2					
Before Infusion					
6	3700	46	2695	2695	0
3	3450	47	2600	2600	0
After Infusion					
3	3575	51	3150	2650	500
8	3570	51	3180	2675	505
48	3875	43	2465	2165	300
86	3700	44	2450	2220	230
107	3510	44	2400	2300	100
127	....	48	....	....	0

mass, and, by the 38th day it had returned to the preinjection level. The hematocrit had also returned to normal by this time. Although the hematocrit and red cell mass had returned to the preinjection levels, this was not due to an increased destruction rate of the infused cells but rather to a concomitant decrease in the recipient's own cells. Thus, while the subjects own red cell mass was about 1800 ml. during the control period, it was only about 1300 ml. at the 38th day post infusion.

As may be seen in the lower half of Fig. 3, the observed survival of the infused cells followed the theoretical line of a normal rate of 0.8 per cent

destruction per day closely. The survival, then, of the infused cells was normal. The subject's own cell mass was not maintained at a relatively constant level (as during the control period), but fell progressively at first, and, in fact, fell at about the same rate initially as did the infused cell mass. When the total red cell mass, donor and recipient, had returned to the preinjection level, this level was thereafter maintained.

It would appear that the initial fall in the subject's own red cell mass following the erythrocyte infusions was due to a decrease in erythropoiesis rather than increased destruction of the recipient cells. Fecal urobilinogen (Fig. 6 and Table VII) excretion was consistent with destruction of the increased total red cell mass at a normal rate, not an increased rate.

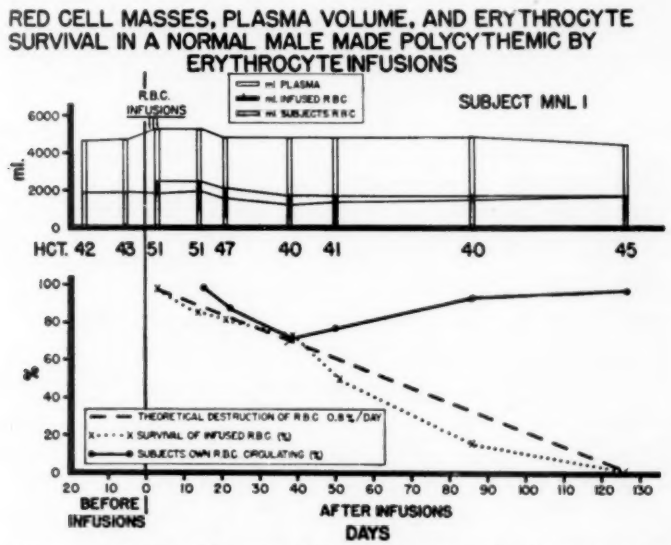

FIG. 3.—Plasma volumes, hematocrits, and red cell masses in a normal male made polycythemic by erythrocyte infusions. The survival of the infused red cells is normal. There is an initial fall in the subject's own red cell mass during the first 38 days following infusion. Thereafter, the recipient cell mass increases progressively to its preinjection level.

Similar findings were observed in subject MNL 2 (Figs. 4 and 7, Tables VI and VII) but the initial fall in the level of the subject's own red cell mass was less marked. This difference can be correlated with the amount of red cells infused (Fig. 5). The first subject received infusions amounting to 40 per cent of his original red cell mass, and demonstrated in essence apparently complete marrow depression, while the second received infusions amounting to 20 per cent of his original red cell mass and demonstrated about 50 per cent marrow depression. The apparent depression of erythrocyte production was only temporary, since as soon as the total circulating red cell mass was returned to the preinjection level, erythrocyte production proceeded at about a normal rate.

C. *Liver Function.* In Table VII and Figs. 6 and 7 are plotted observations of liver function and fecal urobilinogen excretion. Thymol turbidity, thymol flocculation, and serum bilirubin, direct and total, were normal throughout the period of study in both subjects as was the bromsulfalein test in subject MNL 2. In subject MNL 1, the 45 minute bromsulfalein retention rose to about 10 per cent eight days after infusion and persisted at about this level for 50 days, following which it returned to normal. In this subject the bromsulfalein retention had been, on one occasion, just before infusion, 7 per cent. Neither subject developed signs or symptoms of homologous serum jaundice.

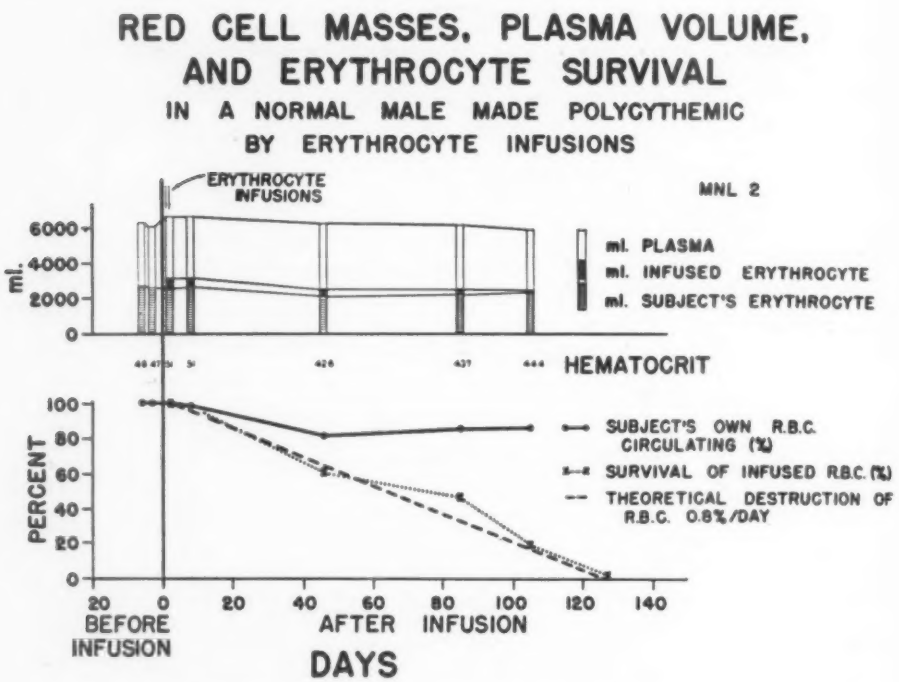

FIG. 4.—Plasma volumes, hematocrits, and red cell masses in a normal male made polycythemic by erythrocyte infusions. The survival of the infused red cells is normal. There is an initial fall in the subject's own red cell mass during the first 48 days following infusion. Thereafter, the recipient cell mass increases progressively to about its preinjection level.

D. *Source of the Extra-Urinary Nitrogen Appearing After the Erythrocyte Infusions.* As indicated earlier, following the infusions of erythrocytes, there was a slow, steady excretion of "extra" urinary nitrogen of 0.5 to 1.0 Gm. per day over the preinjection mean values, which continued for about one month. During this time nitrogen mathematically equivalent to about 80 per cent of the infused red cell nitrogen was excreted. The infused red cells, however, were not the direct source of the "extra" nitrogen. In Figs. 8 and 9 this "extra" nitrogen is plotted cumulatively, and the quantities of nitrogen equiv-

alent to the destroyed infused cells and the reduction in the recipient's own cell mass are also charted.

As pointed out earlier, the observations of cell survival are consistent with normal survival of the infused red cells. As expected, the nitrogen equivalent of the observed decrease in the infused red cell mass agrees strikingly well with the calculated theoretical equivalent, assuming destruction of the infused

TABLE VII.—*Liver Function and Fecal Urobilinogen Excretion in Normal Males Made Polycythemic by Erythrocyte Infusions*

Day of Study	Total Erythrocyte Mass (ml.)	1[1] Serum Bilirubin (mg./100 ml. serum)	Total Serum Bilirubin (mg./100 ml. serum)	Bromsulphalein (% retention at 45[1])	Thymol Turbidity (units)	Thymol Flocculation (units)	Period of Study (days)	Fecal Urobilinogen (mg./day)
Subject MNL 1								
Before Infusion								
24	....	0.05	1.0	3	2	0	16 thru 12	125
17	1800	....	...	..	..	..	.....	...
10	....	0.05	1.9	7	3	0	11 thru 7	210
6	1820	....	...	..	..	..	6 thru 1	180
After Infusion								
8	....	0.05	0.6	11	3	0	1 thru 4	170
16	2535	0.07	1.0	..	3	0	5 thru 9	170
22	2175	0.19	1.9	9	4	0	10 thru 14	190
51	1800	0.12	1.9	10	2	0	.....	...
87	1850	0.20	1.6	2	2	0	15 thru 19	185
108	....	0.12	1.6	1	1	0	20 thru 23	195
							24 thru 28	165
							29 thru 33	190
							34 thru 38	175
Subject MNL 2								
Before Infusion								
24	....	0.02	1.4	1	2	0	16 thru 12	155
10	....	0.19	1.5	3	2	0	11 thru 7	155
6	2695	....	...	..	..	..	6 thru 1	120
3	2600	....	...	..	..	..	.....	...
After Infusion								
8	3182	0.10	0.8	6	3	0	1 thru 4	175
16	....	0.20	2.6	..	3	0	5 thru 9	140
22	....	0.30	2.1	3	4	0	10 thru 14	215
48	2465	0.12	1.3	..	2	0	15 thru 19	200
86	2450	0.10	1.1	2	2	0	20 thru 23	115
107	2380	0.12	1.7	1	2	0	.....	...

cells at a normal rate of 0.8 per cent per day. The nitrogen equivalent of the destroyed infused cells thus accounts mathematically for about one-third of the "extra" nitrogen excreted. The remainder was accounted for mathematically, in the most part, by the nitrogen equivalent of the observed decrease in the subject's own red cell mass.

DISCUSSION

Among the many devices which have been employed profitably in elucidating problems of nitrogen metabolism, the use of the balance study has proved to be of great value. By comparing the total output of a given substance with the intake during a given period, although no specific information of intermediary metabolism is gained, an estimate may be had as to the overall metabolic processing of the material under study. The validity of such balance data is predicated on the ability of the investigator to determine with exactitude the metabolically active amounts of the substance under study which have been introduced into and excreted by the organism during a given period. Such determinations include not only accurate chemical analyses of the raw

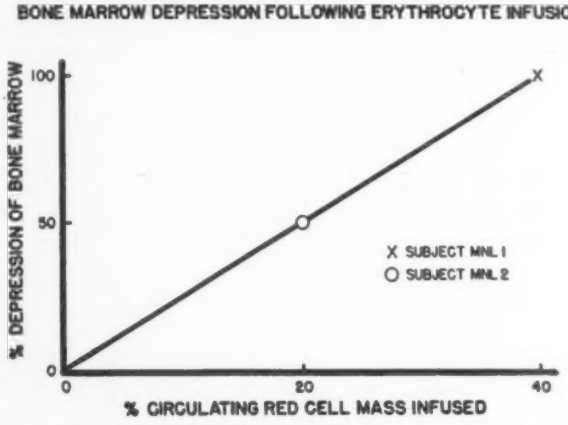

FIG. 5.—Apparent bone marrow depression in normal males made polycythemic by erythrocyte infusions. The apparent bone marrow depression following the erythrocyte infusions was directly proportional to the relative quantity of red cells infused.

materials participating in the balance, but also knowledge of the rapidity with which the nutrient substances actually take part in the dynamics of the metabolic pool. If a material which has been ingested by, or injected into, an animal is not metabolically active during the time of study, it is evident that balances constructed on mere total intake and output data for this period represent mathematical artefacts rather than accurate indices of the actual processing of the nutrient substance.

In the study of protein metabolism, reasonably accurate methods have long been available for the determination of nitrogen content in foodstuffs and excretory products of the organism. The limits of accuracy of such determinations are fairly well known and the significance of data obtained may be scrutinized in light of the probable errors involved. However, in respect to the metabolic fate of a nutrient following its introduction into the organism, knowledge is less complete. It appears that ingested dietary protein, peptides

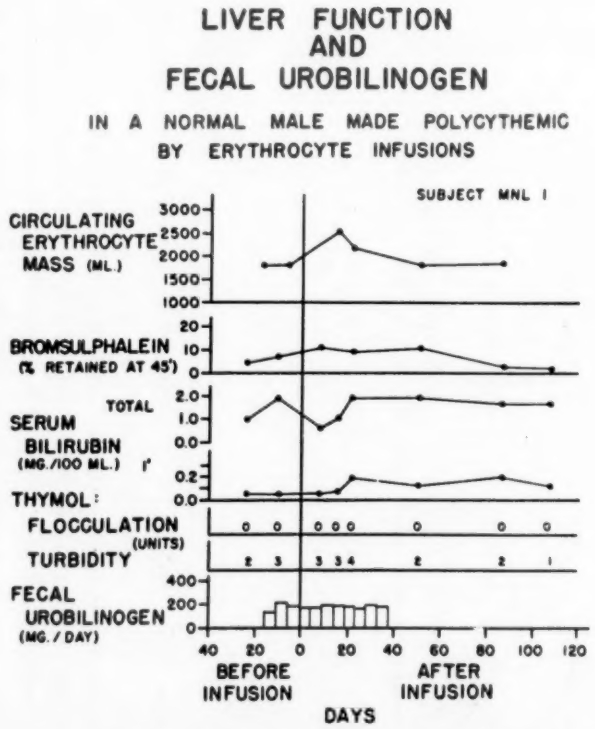

FIG. 6.—Following the infusions, thymol turbidity, thymol flocculation, and serum bilirubin remained normal. The 45-minute bromsulfalein retention was increased slightly during the period eight to 50 days post-infusion. Fecal urobilinogen excretion was not markedly increased following the erythrocyte infusions. This is in keeping with destruction of the increased total red cell mass at a normal, not an increased, rate.

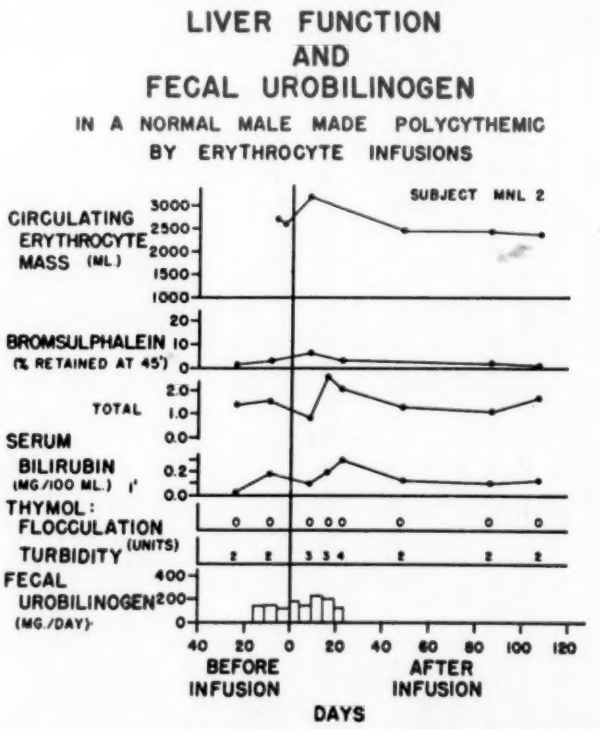

FIG. 7.—Following the infusions, thymol turbidity, thymol flocculation, serum bilirubin, and bromsulfalein clearance remained normal. Fecal urobilinogen increased slightly, quantitatively in keeping with destruction of the increased total red cell mass at a normal, not an increased, rate.

and amino acids are processed rather rapidly. This is suggested by measurement of amino acid levels in the blood following a protein meal[17] and through consideration of the specific dynamic action of ingested protein upon the basal metabolic rate.[18] Such work indicates that the metabolism of the animal begins to feel the impact of ingested protein in a matter of hours, and that its overall fate may be assayed with reasonable accuracy in terms of a few days. The work of Schoenheimer and Rittenberg[19] has conclusively demonstrated that nitrogen ingested as amino acids in the rat is widely disseminated throughout the body within three days following ingestion. It is probable that had their studies been conducted on the basis of shorter time intervals, a still more rapid diffusion of dietary nitrogen would have been demonstrated.

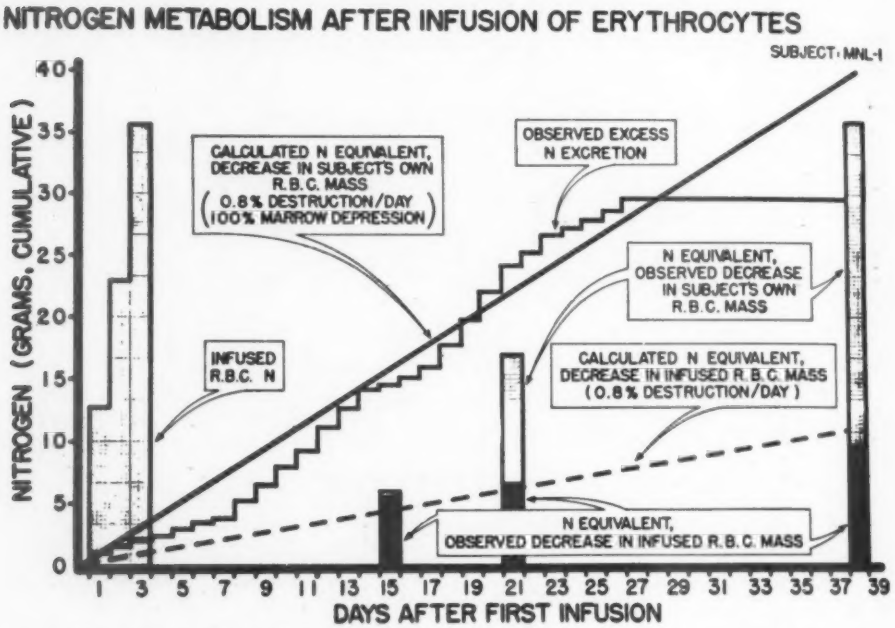

FIG. 8.—(Subject MNL 1) The nitrogen equivalent of the destroyed infused cells accounts mathematically for about one-third of the "extra" nitrogen excreted following erythrocyte infusions in a normal male. The remainder can be mathematically accounted for, in the most part, by nitrogen apparently diverted from normal erythropoiesis.

In recent years, both clinicians and research workers have been assisted by the availability of many nitrogen preparations capable of parenteral administration. Of chief interest among such preparations are four classes of substances: amino acid mixtures, protein hydrolysates (peptides and amino acids), plasma proteins, and whole blood. In regard to the first two classes, it would appear that intravenously injected amino acids and some short chain polypeptides are quickly deaminized or converted into body protein. Injection of such materials finds almost immediate reflection in increased urinary nitrogen excretion in calorically deficient subjects. The greater part of excreted

nitrogen takes the form of end products of protein metabolism (urea and ammonia) rather than of unchanged amino nitrogen. This holds true, in general, only when the natural isomers of the amino acids are used. Unnatural isomers of some amino acids, and certain peptides of some protein hydrolysate preparations are, for the most part, excreted unchanged.

Concerning the use of plasma protein as a source of parenteral nitrogen, it has been demonstrated by Whipple and his colleagues[20] that injection of such material into dogs as the sole source of nitrogen will promote true balance, and, of more importance, will maintain animals in good health over long

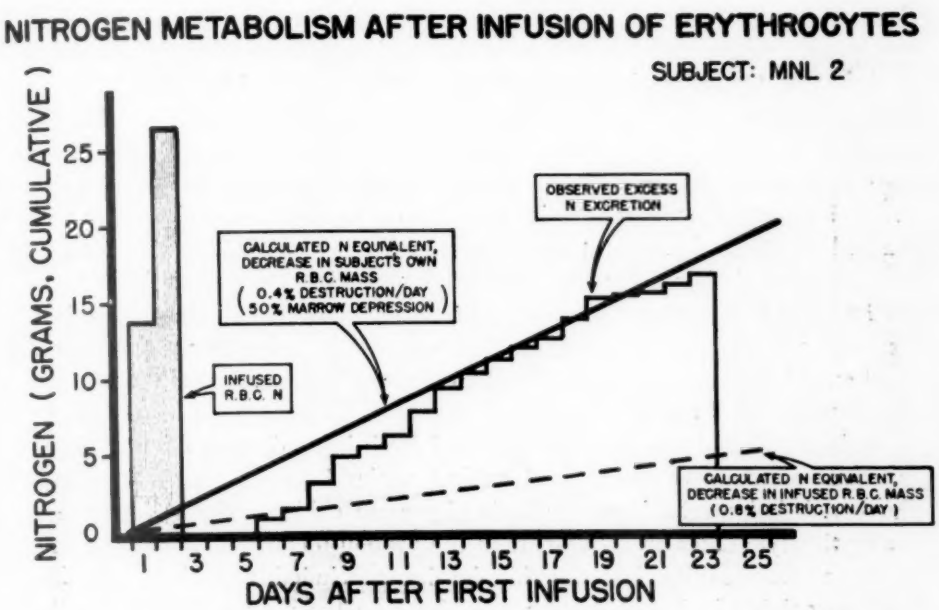

FIG. 9.—(Subject MNL 2) The nitrogen equivalent of the destroyed infused cells accounts mathematically for about one-third of the "extra" nitrogen excreted following erythrocyte infusions in a normal male. The remainder can be mathematically accounted for, in the most part, by nitrogen apparently diverted from normal erythropoiesis.

periods of time. Whipple has also demonstrated,[21] through the introduction of N-15 labeled plasma proteins, that diffusion of the injected protein from the circulation occurs rapidly. Similar results were also obtained by Seligman and Fine[22] using plasma labeled with radioactive sulfur and with bromine. A note of caution in the acceptance of such data as indicating prompt entrance of the injected plasma protein in the metabolic pool, is provided by the work of Albright,[23] Eckhardt[24] and others,[25] who have demonstrated in both normal and hypoproteinemic patients that utilization of injected plasma protein is delayed, ordinarily not beginning until a few days after infusion. Thereafter, the plasma protein is utilized slowly over a period of one or more weeks.

By the use of balance studies, Albright[23] noted that while disappearance of the injected plasma protein from the circulating blood may have been rapid, nitrogen, potassium, sulfur and mineral balances failed to reveal complete "burning" of the plasma or its deposition as body protein until the end of the indicated period. Even if part of the infused material had been immediately incorporated into body protein unchanged, as suggested by Whipple, it appears improbable that such new tissue formation would not have been reflected by changes in the balance of potassium, calcium, phosphorus and sulphur. Similar slow metabolic turnover has also been shown for injected serum albumin.[26] Such a finding as this may in part explain why some investigators have found it relatively easy to achieve *mathematically positive* nitrogen balance with plasma protein or albumin given intravenously. However, it is clear that the immediate metabolic implications of such apparent positive balance are quite different from those of a positive balance attained with oral protein. While such intravenously administered protein may serve as immediate replacement for plasma protein and a source of nitrogen for the organism over a long period, conclusions in regard to its immediate nutritional efficacy reached on the basis of short term studies must be guarded.

Confusion similar to that outlined above has existed in the consideration of erythrocytes as a source of parenteral nutrition. Seriously ill surgical patients commonly receive many blood transfusions, and it is important to know to what extent the erythrocytes of transfusions contribute to the daily nutritional requirements of these patients.

It is established that the life of normal fresh infused erythrocytes injected in tracer amounts to the normal subject varies between 120 to 130 days. Further, it is improbable on the basis of present evidence that the protein of the erythrocyte takes an active part in the protein metabolic pool of the body as long as the red cell is intact. Whipple[20] has concluded from his observations that hemoglobin in its production may draw on the plasma protein but that hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. Moreover, the work of Shemin and Rittenberg[27] with red cells tagged by the administration of N-15 glycine has indicated that, unlike other body nitrogenous compounds, the heme of the red cell retains its labeled nitrogen unchanged throughout its life time. Grinstein, Kamen and Moore,[28] using glycine labeled with C^{14} in the carboxyl position, have shown that the globin moiety of hemoglobin also remains within the red cell during its life span without participating in the dynamic protein interchange characteristic of nucleated cells.

If metabolic effects are to be seen, then, from the infusion of erythrocytes as a source of protein, it would appear likely that these effects must come about either as a result of destruction of the red cell with liberation of its protein for use by the body or from secondary effects of red cell infusions, such as the production of concomitant marrow depression with liberation of the protein ordinarily utilized for erythropoiesis.

In regard to the questions of bone marrow depression and increased erythrocyte destruction, there is evidence indicating that in certain pathologic conditions survival time of the red cell may be materially shortened. Moore and Cope,[29] studying post-burn anemia, were able to demonstrate with the use of radio-iron an apparently increased rate of blood destruction in burned patients. This occurred over and above that noted as a result of the initial hemolysis of erythrocytes produced, probably by the heat, at the time of burning. In addition, these workers felt that some marrow depression occurred in the post-burn state. In regard to other pathologic conditions, Ashby[30] has brought forth evidence that the longevity of the red cell may, on occasion, be materially shortened.

When an actual plethora of red cells exists as opposed to anemic conditions described above, some authors have postulated an increased rate of cell destruction. Earlier experimental work in animals was alleged to have demonstrated this phenomenon.[31, 32] For the most part, rabbits and dogs were used. This early work is open to the criticism that development of isoimmune factors were not given sufficient consideration in evaluation of the data. It is probable that such factors may have played a part in the allegedly increased destruction.

Krumbhaar[33] found that despite the intravenous introduction into dogs of large quantities of nitrogen in the form of whole blood, the total nitrogen, urea, and ammonia in the urine and feces was not appreciably raised for some time after the onset of the plethora. He states that Forster[34, 35] and Tschiriew[36] also had failed to observe an appreciable rise in nitrogen output following homologous blood transfusions in dogs. Miller *et al*[37] have reported studies on one protein-deficient, anemic dog given large amounts of washed red cells intraperitoneally. A total of 163 Gm. of hemoglobin was given and a net production of 173 Gm. hemoglobin and 56 Gm. plasma protein was recorded. This study is difficult to interpret, since it was not possible to differentiate between red cells produced and red cells absorbed intact from the peritoneal cavity. Further, the amount of red cell destruction, which may be fairly considerable when large quantities of washed erythrocytes are given intraperitoneally, was not quantitated.

Kremen[2] in his review outlines the belief of Melnick[38] and associates that "the slow continuous breakdown of injected red blood cells after plasmaphoresis experiments liberated globin which is completely metabolized similar to dietary protein."

In a brief abstract, Taylor and Lytle[39] have expressed the belief that protein of the erythrocyte "is not available for conversion into plasma proteins" over short periods of time. Lacking information as to further experimental details of this study, no statement can be made as to the validity of this conclusion.

Kremen[2] in a short term study of malnourished patients with malignancies infused whole blood intravenously as the sole source of nitrogen intake in amounts sufficient to produce a transient polycythemia. Although apparent

positive nitrogen balance was attained, the red cell protein was apparently not immediately available for general body needs as judged by the failure of extra nitrogen to appear in the urine and the apparent persistence of the infused cells. Pace and his co-workers[40] noted a return of the hematocrit to normal in about 50 days in normal subjects made polycythemic by transfusions. The possibilities of increased cell destruction and/or depressed bone marrow function were discussed, the authors inclining to the latter as more likely. No quantitative assay of bone marrow activity or changes in red cell mass were obtained.

In the present study nitrogen balance and erythrocyte survival in subjects made significantly polycythemic by the infusion of fresh, separated, serologically identifiable red blood cells were followed. Normal adult males at, or near, nitrogen equilibrium were used as test subjects in order to reduce variables to a minimum and to make interpretation relatively straight-forward. When such individuals are on a fixed diet, and the intake of metabolically active nitrogen is suddenly increased, most of the additional intake nitrogen is excreted in a relatively short time, since the body appears to have little capacity for storage of surplus nitrogen under these conditions. By noting the urinary nitrogen excretion following the infusion of erythrocytes, and, in addition, quantitating the survival of erythrocytes, both donor and recipient, it should be possible to estimate the availability of transfused red cell nitrogen to the general body metabolic pool.

Beginning shortly after the infusions in both subjects, extra-nitrogen, 0.5 to 1.0 Gm. daily over and above the preinjection control mean values, appeared in the urine, while fecal nitrogen was unchanged. The increased urinary nitrogen excretion persisted for about one month, following which nitrogen equilibrium was again attained. Although the subjects received different quantities of red cells, and excreted different absolute amounts of excess nitrogen, the excretion was proportionately the same. By the time nitrogen equilibrium was reattained extra nitrogen mathematically equivalent to about 80 per cent of the infused red cell nitrogen had been excreted. The infused red cells, however, were *not directly* the source of the extra-urinary nitrogen. Following the infusions, the initially increased red cell masses and hematocrits fell progressively, and returned to the preinjection level in about 40 days. Pace and his co-workers[38] observed a return to normal of the hematocrit in their transfused subjects in a similar length of time, and concluded that there may have been an increased destruction of infused cells. However, this is not the case. Although the hematocrits and red cell masses returned to the preinjection level, this was not due to an increased destruction of the infused cells. On the contrary, the survival of the infused cells was normal.

On the other hand, the levels of the subjects' own cells were not maintained at first, but fell progressively. This fall appears to have been due to concomitant marrow depression, since it is unlikely that the subject's own cells would have been destroyed at a rate faster than that of the infused cells.

Further, the observed fecal urobilinogen excretions were at levels consistent with normal destruction of the total red cell mass, not increased destruction. The decrease in erythropoiesis was related to the quantity of red cells infused. Thus, the first subject received infusions amounting to 40 per cent of his original red cell mass and demonstrated essentially complete marrow depression, while the second received infusions amounting to 20 per cent of his original red cell mass, and demonstrated about 50 per cent marrow depression. Preliminary examination of sternal bone marrow smears corroborates the apparently diminished erythropoiesis. White cell production was not impaired. The apparent depression of erythrocyte production was only temporary, since as soon as the total circulating red cell mass returned to the preinjection level, erythrocyte regeneration proceeded at about a normal rate. More prolonged marrow depression than was observed in this study has been reported following multiple transfusions in a patient with transient thrombocytopenic purpura.[41] The pathogenesis of marrow depression under the conditions of artificially induced polycythemia outlined in the present study is not clear. It has been suggested[42] that erythropoietic activity may be related inversely to the blood oxygen content.

As earlier indicated, extra nitrogen, mathematically equivalent to about 80 per cent of infused red cell nitrogen, was excreted in a period of a month following the infusions. Quantitatively, however, the nitrogen equivalent of the destroyed infused cells accounted for only about one-third of the extra nitrogen excreted. The remainder could be accounted for, in the most part, by the nitrogen equivalent of the observed decrease in the subject's own red cell mass. It would appear, then, that the observed excess urinary nitrogen following erythrocyte infusions in normal males on a fixed, adequate diet derives in part from the infused red cells, and in part from nitrogen diverted from normal erythropoiesis. It is not implied that the nitrogen appearing in the urine is specifically that of the infused red cells, or that which has been diverted from red cell synthesis, but rather that quantitatively equivalent amounts are involved. The well-known interrelationships of the body nitrogen metabolic pool would negate strict identity.

It is not possible to state with assurance the effect on nitrogen metabolism of the brief influenza-like illness which occurred shortly after the infusions. It is our impression that considering the mildness of the attacks, the effect was minimal and does not introduce any serious difficulties into the interpretation of the study.

It should be pointed out that the quantity of nitrogen which might be available as a result of depressed erythropoiesis even if complete, is small, amounting to only about one Gm. per day. Only a similar relatively small quantity can be expected from the normal breakdown of infused cells. Further, the biologic efficiency of liberated globin as a protein food-stuff in man is not established.[43-45]

It is clear that nitrogen made available to the metabolic pool as a result of erythrocyte infusions is not great, is made available only over a period of weeks, is of unknown biologic efficiency, and quantitatively would contribute little to the overall nutritional requirements. Whether this process is accelerated in patients during catabolic or anabolic conditions is to be studied.

CONCLUSIONS AND SUMMARY

The metabolic fate of infused erythrocytes in adults made significantly polycythemic by transfusions has not been known. Only inadequate and incomplete information has been available on erythrocyte survival and bone marrow function in such individuals. Data on these points were obtained in two normal adult males on a constant diet receiving serologically identifiable, fresh, separated erythrocytes. Observations were made on body weight, nitrogen balance, circulating plasma protein and erythrocyte mass; erythrocyte survival; serum bilirubin concentration; urobilinogen excretion; and liver function.

Plasma volumes, liver function, and circulating plasma proteins were essentially unchanged throughout the period of the study. Survival time of the infused erythrocytes was not shortened. The infused red cell mass decreased at a normal, expected rate of 0.8 per cent per day. Concomitantly, the mass of the recipient's own erythrocytes declined at a rate of 0.4 to 0.8 per cent per day in direct proportion to the relative amount of the infusions. This progressive fall in the subject's own erythrocyte mass was probably due to erythropoietic depression rather than to abnormally increased destruction. This is suggested by the normal survival of the infused erythrocytes and by urobilinogen excretion consistent with breakdown of the total red cell mass at a normal, not an increased, rate. There was a direct linear relationship between the extent of apparent bone marrow depression and the degree of induced polycythemia.

A slow, steady excretion of 0.5 to 1.0 Gm. of nitrogen per day (above the control equilibrium value) began shortly after the infusions and continued for one month. The total extra nitrogen excreted was mathematically equivalent to 80 per cent of nitrogen content of the infused erythrocytes. However, this excess nitrogen derived only in small part from the infused red cells. The greater part could be accounted for almost completely by nitrogen diverted from normal erythrocyte synthesis as a result of apparent marrow depression.

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DISCUSSION.—DR. CHARLES C. LUND, Boston, Mass.: Dr. Levenson and his associates should be congratulated on this careful and rather complicated piece of work. When Dr. Levenson was working with Taylor and me and others of my associates during the studies of burns during the war, Taylor and I had many battles as to what to do with charting the nitrogen that went into these patients in the form of whole blood. However, what you do about getting up your records is not as important as what happens to the patients and what this means to the patients.

The members of this Society, with a long series of studies presented by Elman and Ravdin and others on nitrogen metabolism and studies concerned with transfusion, have a pretty clear idea that blood and nutrition both are needed in the long-time very sick patient. As I talk with people and see patients, a little away from the top medical centers, there still are a great many doctors who know that patients need to be fed, but they don't know the quantitative implications of feeding when continuing losses are taking place, and they are satisfied that they are doing enough to feed the patient if they give a unit or two of plasma, or give some blood. It is surprising how frequently you run into patients who could easily be given either oral or other feeding by those doctors who are perfectly happy that they are taking care of the patients with blood.

This paper is one more to show that the treatment for lack of blood and the treatment for lack of food must be clearly differentiated, and you cannot use one for the other.

DR. F. ROSS BIRKHILL, Chicago, Ill.: I wish to thank Dr. Lund for his helpful comment and criticism of this work. In summary, it should be emphasized that the nitrogen available from erythrocyte infusions may be considered to come from two sources—either from destruction of the red cells themselves or from concomitant marrow depression. We have shown in this study that significant marrow depression indeed does occur, as evidenced by a fall in the erythrocyte mass of the recipient.

We found, as a result of marrow biopsies, that the myeloid-erythroid ratio was materially changed as a result of these infections, and definite marrow depression resulted. A certain amount of nitrogen is to be expected from such depression, and many glowing reports have appeared in the literature postulating a flood of nitrogen from such marrow depression; but it is evident that the erythropoietic centers, which have been accustomed to maintaining a normal red cell volume, can release about 1 Gm. or at the most 1½ Gm. of nitrogen daily.

As a result of this, it is perfectly evident that the amount of nitrogen available from some such erythrocyte depression is inconsequential in providing for the nutritional needs of the patient or in reversing the catabolic phase.

The other source of possible nitrogen, of course, lies in the destruction of the red cells themselves; and we have shown here that such destruction is roughly normal in normal subjects made polycythemic. That increased destruction may on occasion occur in other patients, debilitated, and the like, cannot be denied. Winifred Ashby has put forth evidence to indicate that in various pathological states increased destruction of infused red cells may occur. It has been brought forth many times also that in the post-burn phase, long after the acute thermal trauma to red cells, there occurs a continuing destruction of red cells, at times up to 200 cc. of red cells per day.

However, it is very doubtful that such a condition obtains in the variety of conditions with which the surgeon is faced in his nutritional requirements. Therefore, it may be said that the red cell infusions really mean relatively little to the patient from the standpoint of released nitrogen.

As Dr. Lund has emphasized, it is of no consequence to him that a mathematically positive balance has been maintained by the surgeon. The important factor is whether or not the infused protein is immediately available for his nutritional needs and for the reversal of the catabolic phase, which, as can be seen from previous discussion, probably cannot be varied as an entity as yet.

Therefore, with this evidence we must view with some caution studies in the literature which have reported to reverse catabolic phases, which have purported to maintain patients in good nutritional balance when red cells have been used as a significant part of their daily nitrogen requirements. Before we can evaluate properly such studies, we must know the extent of marrow depression, if any, which has been consequent upon such infusions.

In all probability the nitrogen released is insignificant. We must know the amount of red cell destruction. It appears likely that in the majority of conditions the nitrogen thereby released is also insignificant for nutritional needs, and, lastly, we must know more of the biological value of the red cell protein, namely, globin, for it has been shown to be an incomplete protein lacking certain of the essential amino acids.

Until such information is forthcoming we must hesitate to evaluate finally such studies.

AN EVALUATION OF OXYGEN THERAPY*

PHILIP B. PRICE, M.D., RALPH C. RICHARDS, M.D., AND JAMES B. HAMMOND, M.D.

SALT LAKE CITY, UTAH

OXYGEN IS USED extensively as a therapeutic agent, but not always with discrimination.

The usefulness of oxygen administration has long been a subject of investigation and discussion. Although its theoretical limitations are set forth in textbooks of physiology, and Goodman and Gilman[1] state clearly that "with few exceptions, the therapeutic usefulness of oxygen is in anoxic anoxia," yet in practice, oxygen is customarily administered for all sorts of conditions—to almost any patient, indeed, whose vital functions are threatened. In an influential article, Boothby, Mayo and Lovelace[2] assert that administration of 100 per cent oxygen combats shock, and they recommend the employment of oxygen immediately after operation in all patients who have undergone extensive surgical procedures. Judd[3] is quoted as saying: "There can be no question that the use of oxygen is a valuable aid in the immediate postoperative care of patients for which surgical treatment has been carried out on account of some serious abdominal conditions." The new generation of physician-anesthesiologists are enthusiastic and generous users of oxygen. On the other hand, Blalock[4] expresses the clinical experience of many surgeons when he says, "Inhalation of oxygen in the treatment of traumatic shock has been disappointing."

On theoretical grounds it has been urged that administration of high concentrations of oxygen raises the oxygen content of hemoglobin slightly, and the oxygen content of plasma even more; that is to say, when the patient breathes pure oxygen, his blood may contain up to one-seventh more oxygen than when he breathes air. That would appear to be a worthwhile gain for any patient threatened with anoxia.

The answer to that line of reasoning is that oxygenation is a very complex physiologic and physico-chemical process. Oxygen tension in the blood leaving the lungs is only one of many interrelated variables. There are also matters of adequate respiration, integrity and efficiency of the circulation, ability of blood to give up oxygen to the tissues, and ability of the tissues to utilize delivered oxygen. None of these aspects taken alone can be considered a reliable indication of the degree of oxygenation as a whole. A slight increase in oxygen content of arterial blood, for example, might be more than counterbalanced by a concomitant slowing of the blood flow.

The only single test that provides an accurate measure of oxygenation as a whole is the minute volume of oxygen uptake. Since the body cannot store oxygen, the quantity of gas absorbed by the lungs in a period of time represents the exact quantity used by the body during that time. Oxygen consumption is the algebraic sum of all the variables influencing oxygen utilization.

* Read before the American Surgical Association, April 22, 1949, St. Louis, Missouri.

If the beneficial effects of oxygen therapy are due to an increase in total oxygen consumption, then there should be a measurable difference between oxygen consumed by an individual breathing air as compared to the same individual breathing pure oxygen. It was with this idea in mind that the following study was begun.

TABLE I.—*Peripheral Circulatory Failure.*

Produced by	Effects of Oxygen
Hemorrhage Extensive burn Intestinal obstruction General peritonitis Crush of extremities Histamine injection	No appreciable clinical improvement No significant increase in oxygen uptake

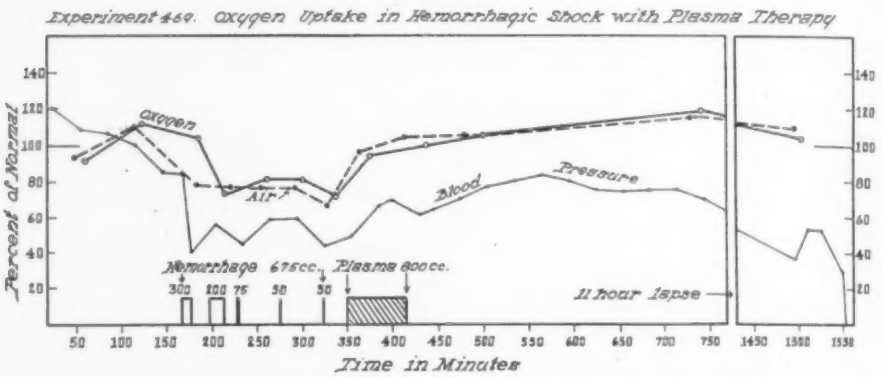

FIG. 1.—A representative experiment in which severe hemorrhagic shock was treated with plasma with temporary improvement but fatal outcome, as indicated by the blood pressure curve. The heavy solid line (labeled "oxygen") indicates the oxygen uptake when the dog was breathing pure oxygen; the broken line (labeled "air") represents oxygen uptake when breathing atmospheric air. It is obvious that throughout the experiment, during the basal period and also during early and late shock, oxygen consumption was similar when breathing air and breathing oxygen.

EXPERIMENTS

Oxygen uptake was measured in about 75 narcotized dogs which were made to breathe first atmospheric air and then approximately 100 per cent oxygen. The gases were administered alternately in accurately measured amounts through a closed system, in which was incorporated a pair of calibrated, water-sealed, BMR spirometers connected to the animal by a cuffed endotracheal tube.

Experiments were in three groups. First, shock was produced in several different ways (Table I). In none of these experiments, during either early or late shock, was administration of oxygen followed by any apparent clinical improvement, or any significant increase in oxygen uptake.

Figure 1 illustrates a typical experiment. This dog was bled severely. When his condition became critical, he was given plasma which prolonged his

life although he died eventually from peripheral circulatory failure. Throughout the experiment, breathing oxygen and breathing air were equally efficacious.

Figure 2 shows a similar result in an animal which, after bilateral lumbar sympathectomy, was subjected to compression of both thighs. A typical acute crush syndrome ensued which was rapidly fatal. Again, it will be noted that breathing air and oxygen had equal effects upon oxygen uptake.

In our second set of experiments (Table II), central circulatory failure was produced by cardiac tamponade. Pressure of fluid in the pericardium was

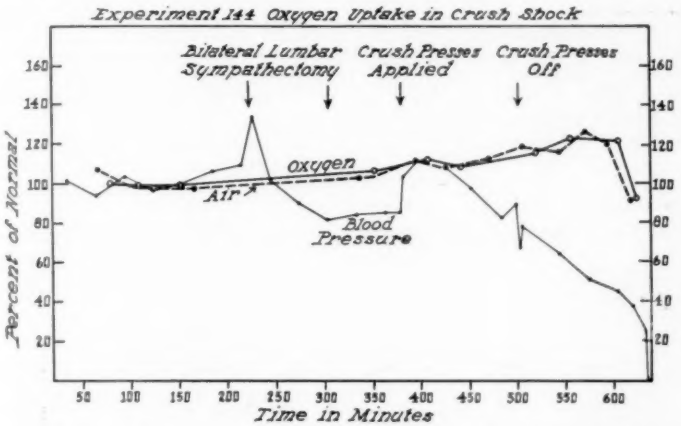

FIG. 2.—A representative experiment in which, following lumbar sympathectomy, crushing force was applied to the dog's thighs for 2½ hours. Rapidly fatal shock ensued. Throughout this experiment air-breathing and oxygen-breathing had equal effects, as far as oxygen consumption was concerned.

TABLE II.—*Central Circulatory Failure.*

Produced by	Effects of Oxygen
Cardiac tamponade	No appreciable clinical improvement No significant increase in oxygen uptake

increased by increments until the animals finally died. In this condition also, administration of oxygen did not improve the animals clinically, and did not increase oxygen consumption.

In a third group of experiments (Table III), respiration was embarrassed in various ways: by tracheal obstruction, by prolonged inspiratory resistance, by pneumothorax and hydrothorax, by central respiratory depression with morphine and barbiturates, and by external pressure on the thorax and abdomen. In mild degrees of respiratory interference, without cyanosis, breathing pure oxygen was of no appreciable value. When respiratory embarrassment was enough to cause slight cyanosis, oxygen relieved the cyanosis, although oxygen consumption per minute was not increased. In severe degrees of respiratory dysfunction, however, oxygen improved the cyanosis and caused a significant increase in oxygen uptake.

Figure 3 illustrates a representative experiment in which we made the dog breathe against inspiratory resistance in an unsuccessful attempt to produce pulmonary edema. It is clear that in this condition oxygen consumption was increased by oxygen administration, although there was a manifest tendency toward compensation, so that after a time air-breathing became just as effective as oxygen-breathing. It will be noted also that sudden falls in blood pressure occurred whenever oxygen was given.

TABLE III.—*Respiratory Dysfunction.*

Produced by	Effects of Oxygen
Central respiratory depression	In mild respiratory embarrassment (without cyanosis), no appreciable benefit
Tracheal obstruction Prolonged inspiratory resistance	In moderate respiratory embarrassment (with cyanosis), cyanosis relieved, but no increase in oxygen uptake
Pneumothorax or hydrothorax Constriction of chest and abdomen	In severe respiratory embarrassment, cyanosis reduced, clinical improvement, increased oxygen uptake

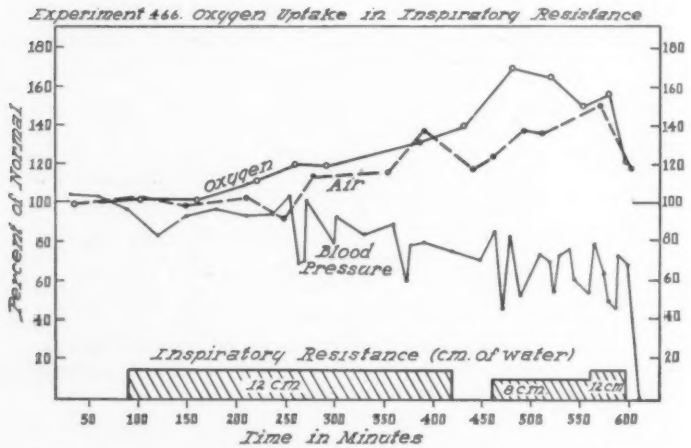

FIG. 3.—A representative experiment in which the dog was made to breathe against inspiratory resistance for many hours. The rising curve of oxygen consumption indicates increasing demands for oxygen that could not be met during the last 2½ hours, in consequence of which the animal died from anoxia. It is clear that breathing oxygen was of some benefit in this case.

Another example of respiratory embarrassment is shown in Figure 4. The aforementioned effects of oxygen are again clearly demonstrated. With a moderate-sized pneumothorax there was slight cyanosis which was relieved by oxygen, although oxygen uptake was not increased. When the pneumothorax was increased, however, so as to cause severe embarrassment of respiration, the benefit from breathing oxygen became obvious, both in clinical improvement and in increased oxygen consumption. But here again, compensa-

tion occurred so that in the end air nearly matched pure oxygen in efficacy. Note also how the arterial blood pressure fell precipitately 20 to 40 mm. Hg. whenever oxygen was given, but rose promptly to its original level whenever the animal was permitted to breathe air again. This last effect was due, we believe, to the fact that the dogs, when given oxygen, breathed much more slowly and easily, but in the process the pumping action of dyspnea on venous return to the heart was largely lost. These drops in blood pressure were associated with, and in fact were caused by, proportionate sudden reductions in cardiac output.

We have had a number of dogs in late stages of shock, with coincident hypotension and respiratory embarrassment, that died suddenly upon administration of pure oxygen. On at least two occasions I have seen the same thing happen in patients. It is possible that in such cases breathing oxygen caused sudden fatal reduction of cardiac output.

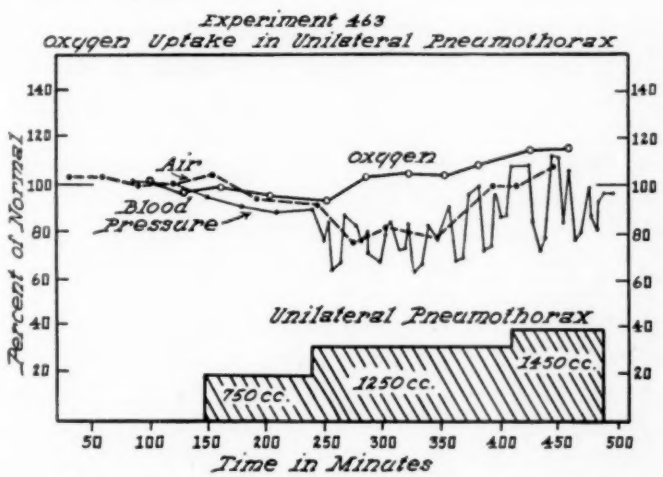

FIG. 4.—A representative experiment in which respiration was embarrassed by pneumothorax. The advantage of breathing oxygen under these conditions is manifest.

DISCUSSION

These experiments are believed to provide at least a partial answer to the questions, What are the indications for oxygen therapy? What does breathing oxygen actually accomplish?

In states of shock in which respiration remains unimpeded, administration of oxygen is of dubious value. Anoxia may indeed be present to a dangerous degree, but breathing oxygen will not correct it. In such cases, time and effort would be better spent in giving blood and blood substitutes, and in other measures designed to improve the failing circulation; for that is where the trouble lies. Restoration of an adequate circulation is the surest way—indeed, it is the only way—to correct the anoxia of shock.

Likewise, in cardiac tamponade, and presumably in other forms of cardiac failure also, if there is no associated pulmonary edema or other abnormality hindering respiration, administration of oxygen has limited value. Here again, the fault lies, not in failure of the blood to be fully loaded with oxygen as it passes through the lungs, but in deficient transportation of the oxygenated blood. In central circulatory failure, therefore, one's efforts should be directed principally toward improving the patient's depressed circulation and reducing, at least temporarily, his total oxygen requirements.

But if, for any reason, free and normal respiration is seriously interfered with, administration of oxygen is nearly always indicated. The greater the respiratory embarrassment, the more urgent the need of breathing oxygen. Even under these circumstances, however, oxygen administration is only palliative. The basic problem is to correct the respiratory dysfunction.

In "admixture cyanosis," in which a portion of the circulating blood passes, without being oxygenated through a non-functioning part of the lung, and returns to the left side of the heart to be mixed with oxygenated blood from the normal lung tissue, oxygen should be used, although the results are apt to be disappointing.

When circulatory failure and respiratory difficulty or disease coexist, oxygen should be given—with caution—perhaps combined with a judicious use to carbon dioxide. But here also it is a mistake to expect too much of oxygen. The best that can be hoped for is to tide the patient over a brief critical period while efforts are being made both to re-establish an adequate circulation and to relieve the respiratory embarrassment.

Although the term *anoxia* is used freely, even glibly, nowadays, actually it is often quite difficult to detect its presence or assess its degree. In extreme cases, such as in asphyxia or acute pulmonary edema, one glance at the deeply cyanotic terrified patient struggling for breath will suffice to establish a diagnosis of severe oxygen deficiency, but in other instances, a dangerous degree of anoxia may exist without any other manifestation than progressive deterioration of the patient's condition.

Symptoms of acute oxygen lack noted by aviators—lassitude, headache, altered respiration, fatigue, and psychic impairment—are not pathognomonic, for they commonly occur without anoxia. Dyspnea more often than not is simply a compensatory reflex act which successfully protects the body from anoxia. Cyanosis is not an infallible criterion. In polycythemia, it may be falsely present; in anemia and in carbon monoxide poisoning, it may be falsely absent; and in individuals with normal blood components, slight cyanosis may only indicate a high coefficient of oxygen utilization. Nor can measurements of arterial or venous oxygen content alone be relied upon to indicate the presence or degree of oxygen deficiency in the body as a whole. That is to say, anoxemia is not a true measure of anoxia.

The problem is complicated further by the uneven distribution of blood in the body, and by regional variations in blood flow. It is quite possible for one

part of the body to suffer oxygen lack while another part receives adequate amounts of oxygen. Blood oxygen measurements in the carotid, for example, or in the lobe of the ear, do not always tell us whether vital centers are or are not receiving all the oxygen they need.

In our present imperfect state of knowledge, the best that can be done, perhaps, is to recognize the problem, utilize all available clinical and laboratory tests, interpret them critically, and exercise diagnostic acumen and clinical judgment. If oxygen lack is suspected, but is thought to be due primarily to circulatory failure, reliance should not be placed on oxygen therapy. If, on the other hand, oxygen efficiency is thought to be present, and to be due primarily to respiratory dysfunction, oxygen should be administered. But in so doing, the weightier matters of correcting a failing circulation and relieving an embarrassed respiration must not be neglected. These we ought to do and not leave the other undone.

SUMMARY

It has been commonly assumed that when oxygen is administered to a patient his total oxygen consumption is increased. Doubts as to the validity of that assumption led to the present investigation.

The value of oxygen as a therapeutic agent was tested directly in animals by having them breathe air and oxygen alternately, and by measuring the amounts of oxygen consumed under comparable conditions.

In shock produced by hemorrhage, burns, intestinal obstruction, general peritonitis, crush of extremities, and histamine injections, administration of 100 per cent oxygen did not result in either clinical improvement or increased oxygen consumption.

Likewise, in central circulatory failure, produced by cardiac tamponade, it could not be demonstrated that breathing oxygen had any advantage over breathing atmospheric air.

However, when respiration was definitely embarrassed by central depression, tracheal obstruction, prolonged inspiratory resistance, pneumothorax, or constriction of the chest and abdomen, oxygen therapy was of demonstrable value. These animals showed clinical improvement, and the total oxygen uptake was increased.

Whenever pure oxygen was administered to dogs with respiratory difficulty, the relief of dyspnea was found to be associated with a fall in blood pressure of 20 to 40 mm. Hg. This effect of oxygen may be dangerous if severe hypotension and dyspnea coexist.

These results should not be surprising. In hemorrhagic and traumatic shock the fault lies primarily in deficient blood volume and depressed circulation, not in failure of the blood to be aerated as it passes through the lungs; whereas, in anoxic anoxia the reverse is the case.

The clinical implications of these experimental observations are discussed.

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DISCUSSION.—DR. JULIAN JOHNSON, Philadelphia, Pa.: Mr. President, I am sure that Dr. Price is correct in his implication that a great many patients receive oxygen therapy when it is not beneficial to them. The inaccuracy of estimation of the arterial oxygen saturation based on the patient's color is well known. An analysis of a sample of arterial blood requires trained personnel and is time consuming.

Perhaps the simplest method of determining whether oxygen therapy is worthwhile is by means of the oximeter. A base line blood analysis is not indispensable. The oximeter can be placed on the patient's ear, and readings made when the patient is breathing air and oxygen. No absolute value of arterial oxygen need be obtained. However, if the relative arterial oxygen is not materially increased when the patient is given oxygen to breathe as opposed to air, it is unlikely that it is beneficial to him. We have used this procedure for some time and have found that we use much less oxygen therapy than previously.

SOURCES OF ERROR IN OXIMETRY*

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THE OXIMETER is a photo-electric device for continuous determination of the arterial oxygen saturation. As the method depends upon the differences in light absorption by the pigments oxyhemoglobin and reduced hemoglobin it is applicable to intact translucent tissue perfused by arterial blood. During the 14 years since the original work of Kramer[1] oximeter technics have been explored which promise valuable clinical adjuncts.[2, 3] In addition to its usefulness for monitoring the surgical patient's condition the oximeter provides theoretically valid determinations of cardiac output,[4-6] oxygen consumption,[7] residual lung volume,[7] saturation time,[8-10] and various circulation time values.[9-13] These convenient rapid oximeter technics should attain wide clinical use with further improvement of the method. Considerable variability in the design of the various oximeters and in the results obtained by different workers necessitated an investigation of the factors influencing oximeter accuracy and reproducibility. This paper is a preliminary report of observations which will be described in further detail subsequently.

In principle the oximeter is a two-color photometer or colorimeter. As in spectrophotometry its operation depends upon the mathematical relationship between the absorption of light and the concentration of the absorbing substance. Ideally, this relationship is logarithmic as defined by Beer's law. In a multi-component system the absorption is additive. Since blood is essentially a two-pigment mixture for purposes of determining saturation, this relationship may be expressed mathematically as:

$$\log \frac{I_o}{I_t} = (\epsilon_1 HbO_2 + \epsilon_2 Hb)\, d$$

I_0 is the incident light, I_t the transmitted light, HbO_2 the amount of oxyhemoglobin, Hb the amount of reduced hemoglobin, and ϵ_1 and ϵ_2 their respective absorption coefficients whose values are constants at a given wavelength. The value d represents the length of the optical path and will also be a constant for this situation.

It is apparent that the amount of light absorbed will be a function of (1) the sum of the amounts of HbO_2 and Hb and (2) the percentage relationship

* Aided by a grant from the National Foundation for Infantile Paralysis. Read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

of these pigments. This implies that it will be impossible to differentiate between changes in the amount of total pigment and changes in the percentage composition merely by measuring light transmission at one wavelength or at one color.

If a measurement is taken at a second wavelength different absorption coefficients for oxyhemoglobin and reduced hemoglobin are obtained which may be used in a similar equation. If the ratio of these two equations is obtained, the result will be found to vary only between two limits representing 100 per cent oxyhemoglobin and 100 per cent reduced hemoglobin respectively, and it will be independent of the total amount of pigment present. Any mixture of oxyhemoglobin and reduced hemoglobin will have its appropriate intermediate value. Mathematically the equation is:

$$\frac{\log \frac{I_{o\lambda 1}}{I_{t\lambda 1}}}{\log \frac{I_{o\lambda 2}}{I_{t\lambda 2}}} = \frac{(\epsilon_{1\lambda 1}\, Hb\hat{}_2 + \epsilon_{2\lambda 1}\, Hb)\, d}{(\epsilon_{1\lambda 2}\, HbO_2 + \epsilon_{2\lambda 2}\, Hb)\, d}$$

The numerators represent the measurements at wavelength (λ) 1 and the denominators the measurements at wavelength 2. The absorption coefficients have characteristic values at each wavelength.

Oxygen saturation is defined as the ratio of oxygen content to oxygen capacity. This can also be expressed as the ratio of oxyhemoglobin to total hemoglobin. One hundred per cent saturation is represented by all the pigment in the form of oxyhemoglobin, and 0 per cent saturation implies that all the pigment is in the form of reduced hemoglobin. Since this is essentially the information obtained by the light absorption measurements, the latter may be calibrated to read in percentage oxygen saturation.

The validity of the above assumptions depends upon the experimental confirmation of the expected logarithmic relationship. Kramer[14, 15] and Drabkin and Austin[16-18] have confirmed the relationship for hemolyzed blood. Its application for oximetry involves light scatter of erythrocytes introducing marked deviations in transmitted light. Thus changes in total blood are not reflected as a linear function of the logarithm of transmitted light. Study of this factor shall be reported subsequently.

The optical density of blood is such in the visible region that only extremely thin cuvettes will transmit significant light. In the red and near infra-red, transmission is considerably higher, permitting the use of thicker cuvettes which are comparable in optical density to the arterialized ear. A region in the near infra-red is known at which the absorption coefficients of oxyhemoglobin and reduced hemoglobin are the same. If this region is used for the measurement at wavelength 2 the denominator of the equation is simplified. In this situation the total hemoglobin may be measured.

The above discussion has been based on established spectrophotometric principles which require that the light be monochromatic, the walls of the

cuvette parallel, the absorbing medium homogeneous, and that no other absorbing elements be present. In practice, oximetry has employed polychromatic light, non-parallel walls for the "cuvette," an unknown homogeneity of the medium, and tissue other than the blood absorbing considerable light. The influence of these deviations from the ideal require investigation for the development of quantitative oximetry.

Polychromatic colorimetry of existing oximeters does not afford a rigorous assay of the variable factors encountered in the transillumination of bloodless and perfused tissue. Complete spectral data pertaining to the oximeter have not been previously reported. Therefore spectrophotometry of the human ear has been undertaken to establish a preliminary working basis for the design of an improved oximeter.

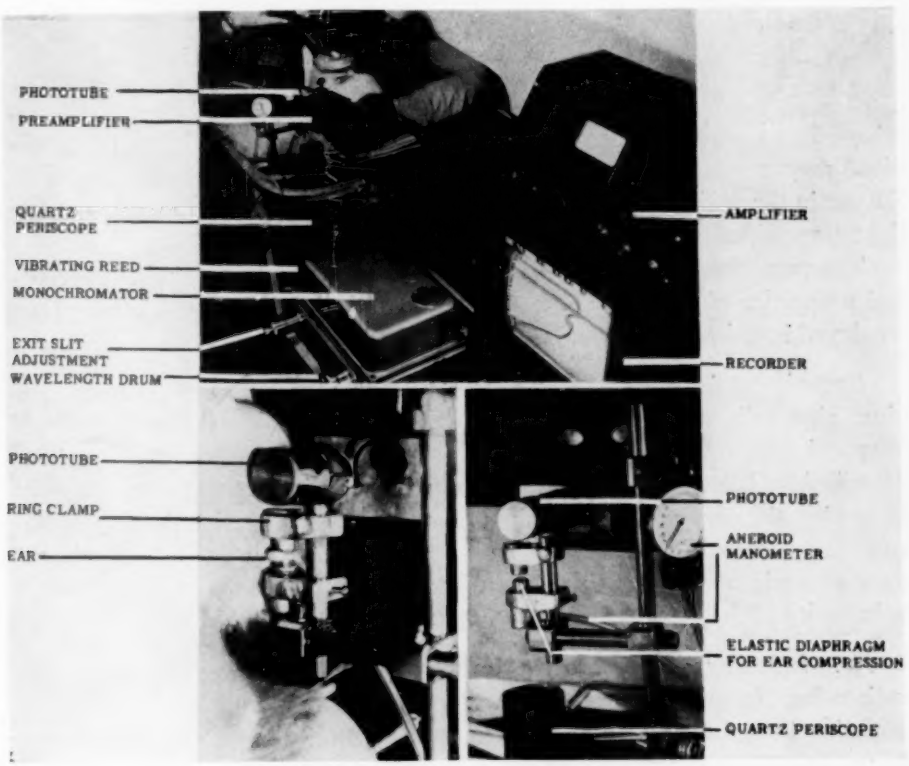


FIG. 1.—Ear spectrophotometer.

METHODS

The ear spectrophotometer. A Perkin-Elmer model 12 monochromator was modified to conduct the light from the exit slit via quartz prism to the ear of a recumbent subject (Fig. 1). A wavelength band of approximately 80 Angstroms in width was required to transmit sufficient light through the ear. An emission type phototube of the S-1 or S-4 spectral response was mounted above the ear to measure the transmitted light. The monochromatic beam was

interrupted at a frequency of 17 cycles per second by a vibrating reed to modulate the output of the phototube. The amplified AC signal was rectified and recorded by a continuous ink-writing potentiometer. The chart speed of the recorder was synchronized with the rotation of the Littrow prism of the monochromator so that the spectrum between 4,000 and 11,000 Angstroms was scanned and the transmission spectrum recorded automatically.* The ear of the subject was secured without compression in a ring clamp in which a transparent plexiglass cylinder covered by a translucent rubber diaphragm was applied to the surface of the ear (Fig. 1). This cylinder was connected to a pneumatic pressure system to allow compression of the ear to an arbitrary pressure of 200 mm. Hg. The spectral transmission of the bloodless and perfused ear were calculated as percentage transmission as follows:

$$\% \text{ Transmission} = \frac{I_t}{I_o} \times 100$$

where I_t represents the recorded value of the transmitted light. I_o for the bloodless ear was taken as the phototube response at each wavelength without the ear in the optical path. I_o for the perfused or flushed ear was taken as the light transmitted at each wavelength by the bloodless ear.

The monochromator described above was also used to determine the spectral properties of various filters, photocells, and phototubes which have been employed in oximeters.

Experimental oximeters. Various earpieces were constructed, using selenium photocells as the light sensitive elements and various Wratten red and infra-red filters to obtain a two-color system. The breaker type amplifier described by Liston and associates,[19] providing low input resistance, was used to amplify the output of the selenium photocells. An Esterline-Angus 5 milliampere continuous ink writer was used as a recorder. The various impedances were properly matched so that the entire unit gave linear response to changes in intensity of the incident light. Figure 2 illustrates this unit.

Arterialization of ear blood. Conventional methods of heating the ear by radiant heat from the light source were employed. In addition, a method of perfusing heated air over the ear was used to study the effects of such conducted heat (superimposed over the radiant heat of the light source) upon the arterialization of the ear blood. Another method for arterialization utilized the local administration of histamine to the ear by electrophoresis as described by Matthes.[7] One cc. of aqueous solution containing 2.75 mgm. of histamine acid phosphate was placed on the positive electrode (1 cm. x 1 cm. in size and covered with blotter paper). The positive electrode was applied to the ear, the negative electrode to the subject's leg. The current was slowly adjusted to

* We are indebted to Mr. Max D. Liston of the Perkin-Elmer Corporation, Glenbrook, Connecticut, for the design, construction, and loan of the ear spectrophotometer.

5 milliamperes at a rate governed by the subject's comfort. Too rapid a change in current produced slight dizziness, apparently due to stimulation of the vestibular apparatus. Electrophoresis was continued at this current 2.5 minutes on each side of the ear. A marked degree of arterial flushing was produced

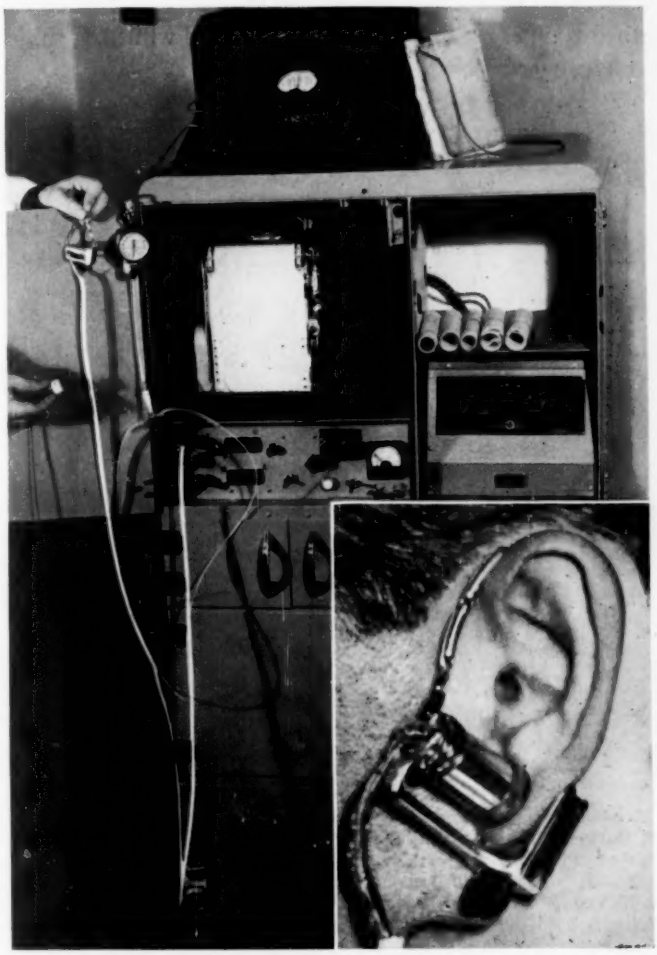


FIG. 2.—Recording oximeter. Galvanic apparatus for histamine electrophoresis appears in upper part of photograph. Operator holds earpiece shown in insert in left hand and the positive electrode for electrophoresis at the ear in right hand.

and maintained undiminished for two to four hours; enlargement and erythema at the site subsided after four to seven hours. No untoward symptoms or residual effects were encountered with this method.

OBSERVATIONS

Studies of the spectral transmission of bloodless ears of normal white male and female subjects revealed no interfering absorption bands of the tissue in

the spectral region between 5300 and 11,000 Å. Figure 3(A) shows a typical transmission spectrum of the bloodless ear of an adult white male. This data was obtained from the cartilaginous helix of the ear. Following determination of the bloodless transmission spectrum with the ear under pressure of 200 mm. Hg., spectra were taken without applied pressure of the flushed ear while the subject breathed 100 per cent oxygen (curve B) and while the subject breathed 10 per cent oxygen (curve C).

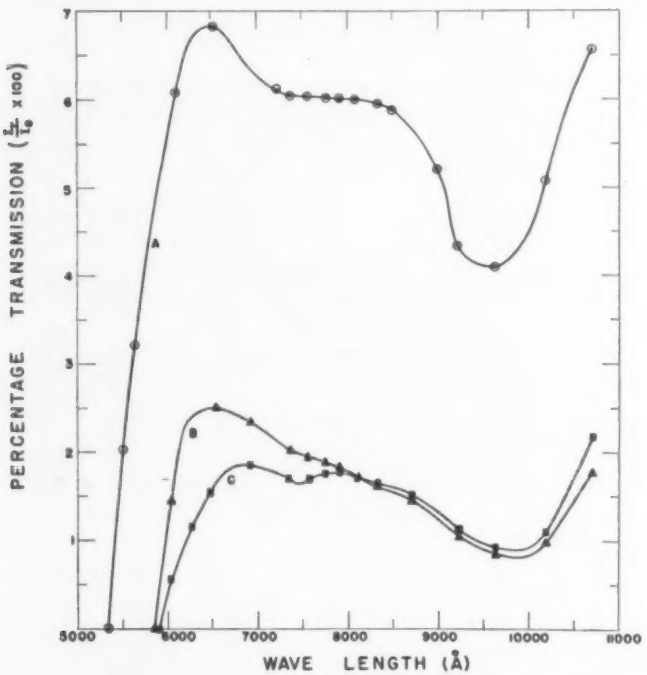
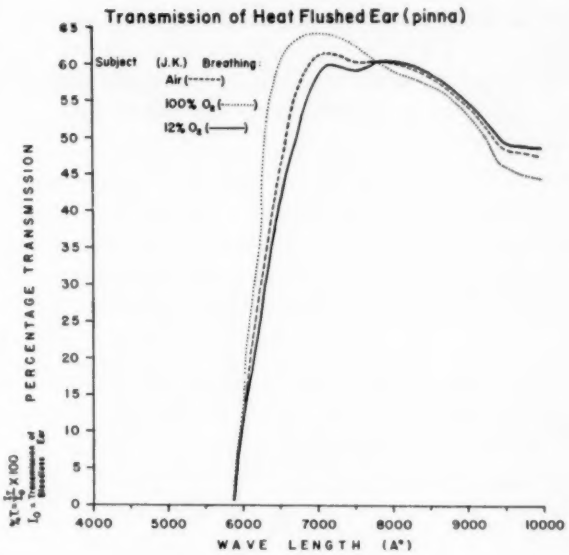


FIG. 3.—Transmission spectra of bloodless cartilaginous helix of normal adult white male (curve A) and of histamine flushed ear of the same subject breathing 100 per cent oxygen (curve B) and 10 per cent oxygen (curve C). A comparison of curve A with curves B and C suggests that some blood remains in the helix at a pressure of 200 mm. Hg.

Transmission spectra of blood in the heated ear of a normal subject breathing air, 12 per cent oxygen, and 100 per cent oxygen are shown in Figure 4. Prior to these determinations the ear was heated by means of an infra-red lamp, and while the spectra were being taken a stream of hot air was perfused over the ear. The heat was applied to the limit of tolerance. This method of arterializing the ear blood differs from the method used in oximetry in which radiant heat from the light source is employed. The latter could not be used in experiments with monochromatic light. The transmission in the red region was highest with the subject breathing 100 per cent oxygen, lowest with 12 per cent oxygen, and intermediate with air. At approximately 7900 Å the three

FIG. 4



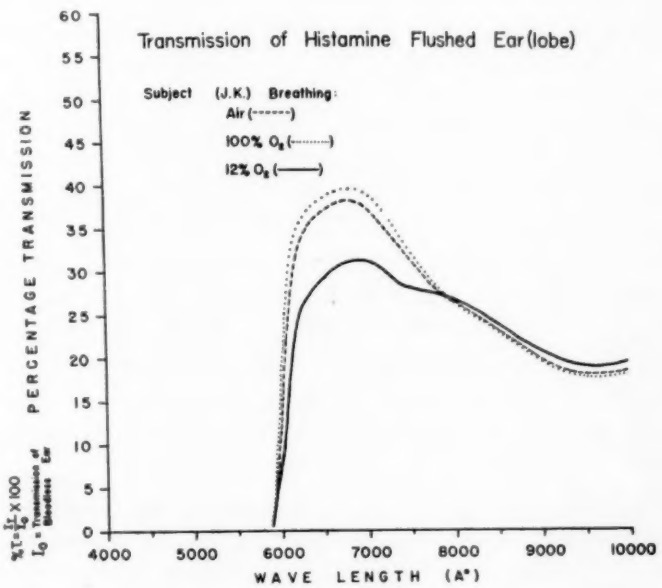


FIG. 5

FIG. 4.—Transmission of the heat flushed ear.
FIG. 5.—Transmission of the histamine flushed ear.

spectra were the same. At longer wavelengths the highest transmission was obtained with the subject breathing 12 per cent oxygen, lowest with 100 per cent oxygen, and intermediate with air. Grossly these spectra resemble those of oxyhemoglobin and reduced hemoglobin. Comparison of the air curve with

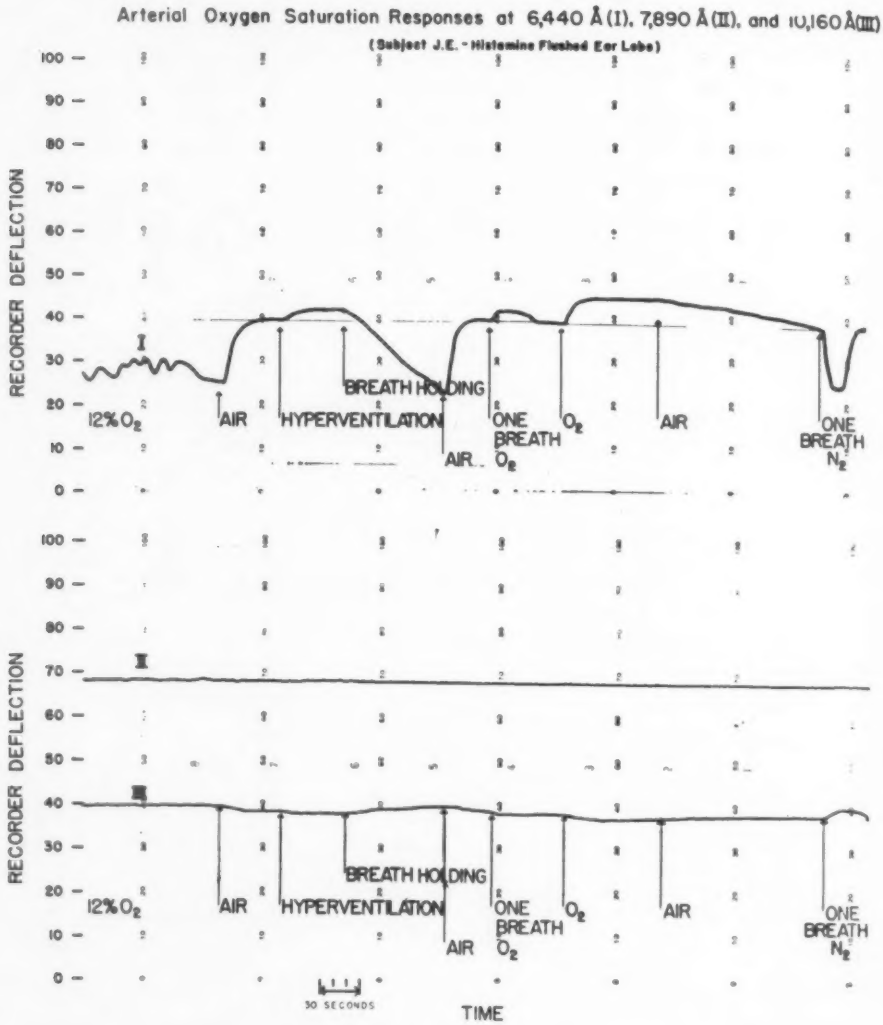


FIG. 6.—Arterial oxygen saturation responses at 6440Å, 7900 Å, 10,160 Å

the 100 per cent oxygen and 12 per cent oxygen curves suggests that the ear blood was not completely arterialized. The air curve should represent a saturation of 97 per cent, the oxygen curve 100 per cent, and the 12 per cent curve 75 to 80 per cent. Actually the air curve deviates inordinately from the oxygen curve and more closely approximates the 12 per cent curve.

Further evidence for this interpretation was obtained in the same subject when the spectra were taken from the histamine flushed ear (Fig. 5). Under these conditions the air curve reasonably approaches the 100 per cent oxygen curve and deviates markedly from the 12 per cent curve. Thus, the histamine flushed ear contained blood more nearly arterial than did the heated ear. A striking feature in the histamine spectra is the greater quantity of blood per unit of tissue as compared to the heat spectra. This observation may be important in oximetry since a greater percentage change in light transmission results from a given change in the saturation. Theoretically, the greater the degree of vasodilatation, the more complete would be the arterialization, assuming no change in arterial pressure. The heat and histamine spectra illustrate the importance of complete arterialization of the ear blood in the oximeter measurement. Variable components of venous blood in the optical path would produce error and defeat reproducibility.

Figure 6 indicates transmission values at fixed wavelengths. Oxygen saturation was changed by allowing the subject to breathe various gas mixtures, hyperventilate, and hold his breath. The wavelengths selected to measure the resulting transmission changes were (1.) in the red region (6440 Å) to obtain large differences in light absorption between oxyhemoglobin and reduced hemoglobin, (2.) in the near infra-red region (at 7900 Å) to obtain identical absorption between the pigments at their "crossover" point, and (3.) in the infra-red region (10,160 Å) to represent the reverse effect in absorption of the pigments at a wavelength longer than that of the "crossover" point. In Curve I marked fluctuations in the transmission occurred with each respiratory cycle while the subject breathed 12 per cent oxygen. When the subject breathed air the transmission value increased and reached equilibrium within 15 seconds. Hyperventilation further increased the value and breath-holding produced a decrease. Breathing air again duplicated the previous response. A single inspiration of oxygen immediately followed by air breathing provided a transient increase in the transmission. The high sensitivity illustrated by this response has not been observed with conventional oximeters in this laboratory. Upon changing from air to oxygen the transmission value again reached equilibrium within 15 seconds. One breath of nitrogen followed by air breathing provided a very steep decrease in the transmission value. These measurements suggest that higher sensitivity could be obtained in oximetry if the red transmission were measured in a narrow wavelength band taking optimal advantage of the difference in light absorption between oxyhemoglobin and reduced hemoglobin. Actually in existing oximeters this measurement has been made using a very broad spectral band (6000 through 8400 Å) which sacrifices this advantage.

Curve II of Figure 6 (taken at 7900 Å) indicated no significant changes in transmission when the subject breathed the same gas mixtures, hyperventilated, and held his breath as in the previous experiment (Curve I). This observation further confirmed this wavelength as a "crossover" point between

oxyhemoglobin and reduced hemoglobin. It also indicated that under the conditions of these experiments no significant changes occurred in the total hemoglobin content of the histamine flushed ear.

In Curve III of Figure 6 (taken at 10,160 Å) the changes in light transmission produced by changes in arterial oxygen saturation were in opposite direction to the changes in transmission measured in the red region (Curve I) and of lesser magnitude.

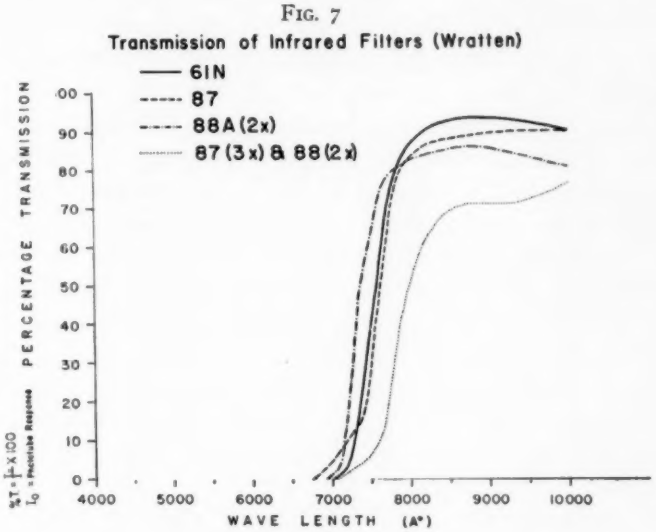
Ideally, the two-color oximeter should provide measurements comparable to those shown in Curves I and II. The red measurement should indicate the maximal differences between oxyhemoglobin and reduced hemoglobin; the infra-red measurement should measure total hemoglobin completely independent of the oxygen saturation.

Figure 7 shows the transmission of varied infra-red filters which have been used in the oximeter. Since selenium photocells are relatively insensitive in the infra-red region an S-1 phototube was used for these determinations. The Wratten 61N filter was first used in the Millikan earpiece; Coleman subsequently substituted the Wratten 87. The modified oximeter of Wood and associates uses two thicknesses of Wratten 88A for the infra-red cell. With the selenium photocells used in this laboratory none of these filters provided an infra-red cell which was independent in output of changes in oxygen saturation. Unfortunately there is considerable variability in near infra-red response of different photocells, so that a filter affording the desired characteristics with one cell may not behave similarly with another. Empirical trial of various filter combinations resulted in the selection of a combination of Wratten filters (No. 87 in 3 layers and No. 88 in 2 layers) which fulfilled the requirement of independence from changes in oxygen saturation. The transmissions shown in Figure 7 show how the short wavelength "cutoff" of these filters is related to the crossover point of oxyhemoglobin and reduced hemoglobin. Comparison of these curves with the spectral response of a selenium photocell (Fig. 8) indicates that shifting the filter "cutoff" short of 8000 Å would provide a greater photocell output at the expense of measuring at the crossover point. Thus, infra-red filters providing a greater sensitivity with selenium photocells introduce the undesirable responses to changes in oxygen saturation. Ideally the infra-red measurement should deal only with total hemoglobin.

Figure 8 compares the spectral response of a selenium photocell to that of the S-1 phototube. At 6500 Å the relative responses of the two detectors are approximately equal, or 40 per cent. At 8000 Å the selenium response is only 3 per cent and the phototube response is 75 per cent. With some phototubes the response is 100 per cent at 8000 Å. The Wratten 29F filter has been used for the red cell in all of the oximeters in this country. There is overlapping between the spectral transmission of this filter and any of the infra-red filters. The advantages of using an S-1 phototube with better isolation of both the red and the infra-red measurements in oximetry appear promising.

Figure 9 shows red and infra-red oximeter responses to changes in oxygen saturation and to changes in ear blood volume. The latter were obtained by Valsalva maneuvers and by Mueller maneuvers, consisting of forced expiration

FIG. 7



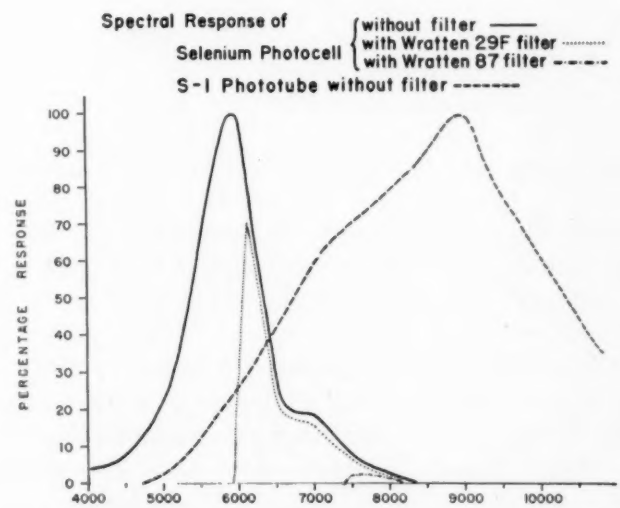


FIG. 8

FIG. 7.—Transmission of infra-red filters.
FIG. 8.—Spectral response of selenium photocell and S-1 phototube.

and inspiration respectively with glottis closed. The unit shown in Figure 2 was employed to amplify and record the responses of the red and infra-red cells. Curve I was obtained with Wratten 87 filter; changes in transmission with changes in oxygen saturation are apparent. This effect was excluded

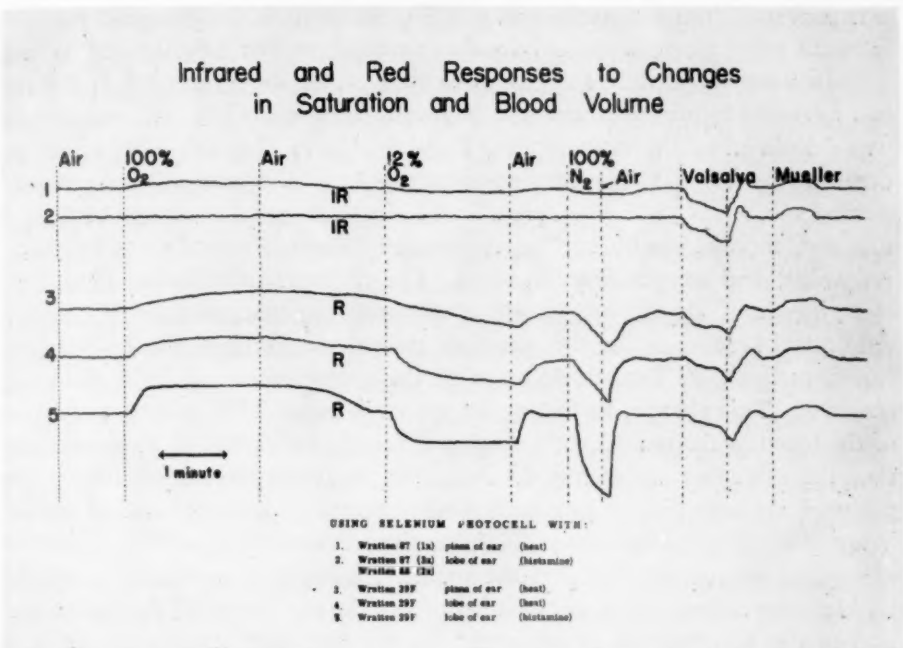
when the filter combination previously described was used (Curve II); however, this unit fortunately retained a comparable sensitivity to changes in total hemoglobin.

Curves III, IV and V of Figure 9 compare saturation responses of the red cell (Wratten 29F) when either heat or histamine was employed to arterialize the ear blood. Curve III was obtained with a Millikan earpiece on the heated cartilaginous pinna. Note the prolonged saturation time of 120 seconds when the subject changed from air to oxygen. Curve IV was obtained with the earpiece illustrated in Figure 2 applied to the heated ear lobe. Here the responses suggest that more arterial blood was present in the optical path since greater deflections occurred with changes in saturation. Curve V was obtained with the same earpiece applied to the histamine flushed ear lobe of the same subject. Remarkably rapid dynamics were recorded when the saturation was changed; these curves actually compared quite favorably with those obtained with the ear spectrophotometer (wavelength at 6440 Å). The saturation time on changing from air to oxygen was 20 seconds. The steep decrease in transmission (Curve V) with nitrogen breathing and the rapid return of the transmission to the previous air value bear a striking contrast to the Millikan measurements upon the heated ear.

Figure 10 compares the rapid desaturation responses obtained by a single maximal inspiration of helium measured with a red cell applied to either the heat flushed or the histamine flushed ear. The breathing maneuver was that employed for the oximetric determination of cardiac output.[5] If the pulmonary mixing of the inspired helium reduces alveolar oxygen tension to that of the mixed venous blood, the oximeter value will reach a "plateau" lasting 6 to 10 seconds, which is then terminated by recirculation. The oximeter shown in Figure 2 was applied to the heated ear lobe of a normal subject. Repeated attempts to obtain the "plateau" were unsuccessful; two of these records are shown in upper Figure 10. Upon completion of each trial when air was breathed the oximeter value did not return to the previous air normal value immediately but required at least two minutes. These prolonged responses were not associated with periodic breathing following the period of hypoxemia. These observations afford another criterion for the presence of venous blood at the site of measurement. In comparison consecutive trials were all successful when the histamine flushed ear lobe of the same subject was the site of measurement (lower Figure 10). Moreover air breathing after each maneuver was followed by a return within ten seconds to the previous air transmission values. Thus, the action of histamine had more completely arterialized the ear blood. In this application of the oximeter this source of error is of prime importance.

Experiments for evaluating the effects of heat in arterializing the ear blood may be summarized briefly. An experimental earpiece was constructed which provided for two independent sources of heating. A conventional Millikan oximeter light source was mounted in the earpiece so that it would be separated

FIG. 9



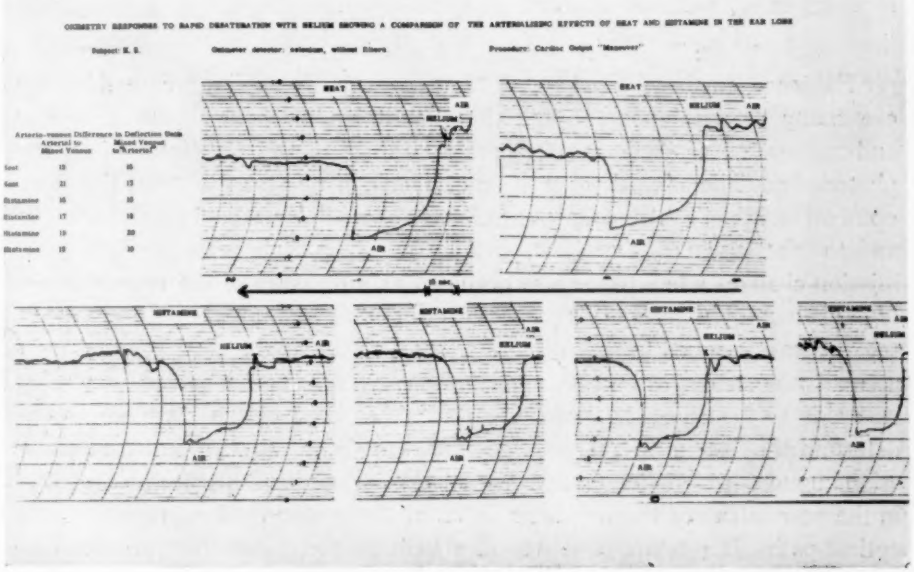


FIG. 10

FIG. 9.—Infra-red and red responses to changes in saturation and blood volume.
FIG. 10.—Oximetry responses to rapid desaturation with helium comparing the arterializing effects of heat and histamine.

from the proximal ear surface by 3 mm.; this unit provided the radiant heat which has been employed in oximetry. In addition the light source enclosure was converted into a system for circulating hot air over the proximal ear surface. In other respects the earpiece was similar to that described by Wood. Bloodless and heat flushed ear transmission values were recorded in the red and infra-red by means of the unit shown in Figure 2. The oximeter output was calculated as the ratio of (log R_0—log R_n) to (log IR_0—log IR_n)* as described by Wood.[2] The earpiece was applied to the cartilaginous pinna of normal subjects, 15 minutes were allowed after the light source was turned on to allow "thermal equilibrium" as evidenced by a constant reading in the infra-red value, and oxygen was breathed. The decrease in oximeter output on changing from air to oxygen was comparable to that obtained by Wood. Additional heating of the ear was then started by means of the hot air perfusion method. A further decrease in the oximeter output was uniformly observed. This change, indicating an apparent increase in oxygen saturation of the blood in the optical path, continued for approximately five minutes and then the value became stabilized. Graded increases in the temperature of the perfused air over the ear produced further decreases in the oximeter output. When this value had become stable for a given temperature the administration of oxygen consistently reduced the oximeter output below that obtained by air breathing. Since this additional heating of the ear increased the arterialization of the ear blood, it is apparent that the previous heating by the light source, per se, had not afforded complete arterialization.

DISCUSSION

Evidence suggests that an absolute quantitative oximeter method may eventually be developed through the elimination of known sources of error and refinement of the measurements according to the principles of spectrophotometry. The clinical value of an oximeter of this type justifies this development. Original contributions to oximetry should be credited to Kramer[1, 13-15] and to Matthes.[20, 21] Earlier studies by Nicolai[22] dealt with the light transmission changes when tissue was occluded as a measure of the reduction time of oxyhemoglobin. Kramer's one-color unit, measuring transmission in the red region, was designed to fit around the intact artery of the dog. It consisted of a small tungsten light source, a selenium photocell, and a galvanometer. He was able to obtain an agreement within 1 per cent of the saturation values determined by chemical analysis. Matthes[21] modified the method for determinations upon the transilluminated human ear and added a second measurement in the near infra-red to provide an index of changes in total hemoglobin in the optical path. His device consisted of a light source, a selenium photocell and galvanometer for the red measurement, and a phototube and galvanometer

* R_0 and IR_0 represent the red and infra-red bloodless transmission values, respectively.

R_n and IR_n represent the red and infra-red "normally flushed" transmission values, respectively.

for the infra-red measurement. Subsequent modifications of the oximeter have incorporated this two-color principle.

Goldie[23] introduced the correction factor for the light absorption contributed by the bloodless ear tissue. The latter was measured by occluding the ear tissue with a movable transparent plunger in the earpiece. His was the only instrument to be described in which the indicated oximeter value represented the ratio of (log R_0—log R_n) to (log IR_0—log IR_n). The latter calculation was performed as a function of electrical circuit and a specially devised ratiometer.

Millikan's oximeter[24] indicated the saturation value as a simple difference between the red and infra-red transmissions, (R_n—IR_n). The log-ratio relationship was abandoned to obtain a simple qualitative instrument for use in altitude physiology. Preliminary adjustment of the oximeter value to that estimated by the operator limited the clinical usefulness of Millikan's device. In patients with arterial hypoxemia, repeated sampling of the arterial blood for chemical analysis was necessary. Without these calibrations for each procedure the Millikan oximeter served merely to indicate changes in the patient's arterial oxygen saturation. Hemingway and Taylor[25] adapted the Millikan instrument for continuous ink recording by means of an amplifier[19] and recorder similar to that previously described (Fig. 2). The oxyhemograph of Hartman, Behrmann, and Chapman[26] is a similar recording instrument. These modifications differ from the original Millikan device primarily in the means used for recording the oximeter value.

The recent work of Wood and associates[2, 27] has revived the bloodless ear tissue correction and the log-ratio relationship employed by Goldie. Their work represents the first major attempt to make the oximeter measurement an absolute determination, permitting estimation within ± 5 per cent of a patient's arterial oxygen saturation, regardless of the degree of arterial hypoxemia.* The evidence of the reliability of their modified oximeter, based on extensive Van Slyke calibrations, suggests that this approach is valid, and that further refinement in the method should lead to higher accuracy.

The studies now in progress which have been described in this preliminary paper represent the first attempt to evaluate the problems in oximetry by means of spectrophotometry. On the basis of these data the selection of optimal wavelengths for the red and near infra-red oximeter measurements may be made. The spectra of the ear reveal no interfering bands of absorption due to tissue in these regions. The use of monochromatic light in the source would appear to offer a greater degree of sensitivity. Although the mathematical relationship, which appears to be valid, relating the light transmission measurements to the oxygen saturation is somewhat complex, it would offer a great convenience in the clinical oximeter to perform this calculation by means of an electronic circuit. Improved components for the instrument which require

* Calibrations in this laboratory of a two-color oximeter similar to that of Wood and Geraci[27] have shown a comparable degree of accuracy.

development may resolve the colorimetric oximeter into an essentially spectrophotometric apparatus.

Failure to obtain complete arterialization of the ear blood represents a major source of error and variability. This factor may involve more than an optimal degree of vasodilatation if the application of the earpiece is such that blood is trapped within the optical path. It would appear that both inadequate arterialization of the ear blood and a limitation of blood flow across the optical path contribute to the prolonged saturation dynamics obtained with the Millikan earpiece. Thus, the saturation time when normal subjects change from air to oxygen has been reported by Fowler and Comroe[8] to average 120 seconds. This agrees with the observations in this laboratory when the Millikan oximeter was used. Wood, Taylor, and Knutson[10] have reported an average of 46 seconds for the saturation time, using the modified oximeter. As indicated in this paper this response is of the order of 15 to 30 seconds when the measurement is made upon the histamine flushed ear. In applications of the oximeter which relate to the dynamics of gas exchange in the lungs it is of prime importance to obtain arterialization of the ear blood.

Recently Wood and associates[6, 10] have reported evidence that the heating technic employed in the modified oximeter earpiece does afford arterialization of the ear blood.* Since the degree of heating in this unit is comparable to that obtained with the Millikan earpiece it would appear that some additional feature in the method of Wood excludes the venous blood from the optical path. The application of the earpiece to the ear at considerable pressure and the initial exclusion of all blood from the optical path by inflation of the pressure capsule may well eliminate the venous component. It should be pointed out that the entire ear is not heated by the light source, so that the blood from adjacent unheated capillaries which is drained by large veins traversing the optical path is apparently the non-arterialized blood in question. Observations described above indicate that the use of heat to arterialize the ear blood is subject to variability greater than that encountered when histamine electrophoresis is employed. If heat is to be employed in oximetry, more data are required to determine the critical threshold for optimal arterialization. Establishing a standardized technic in this regard is essential. Histamine electrophoresis offers the advantages of a more stable local vasomotor state and an increased amount of blood per unit of tissue. The latter factor provides a greater measurable change in light transmission with a given change in the arterial oxygen saturation.

Among other potential sources of error which have not been evaluated is the way in which the two photocells are mounted in the earpiece. In both the Millikan and Wood earpiece the red cell is a narrow central area on either side of which the larger infra-red cells are placed. Whether both cells can view the same sample of blood and ear tissue in the optical path is questionable.

* Comparison of heat and histamine arterialization reported recently by Wood and colleagues has not indicated a significant difference in the two methods.

The fact that the vascularization of the cartilaginous pinna is not one of fine homogeneity further suggests that this factor deserves attention. Another source of error which may be eliminated is the variability in red and infra-red energy emission due to changes in the voltage applied to the light source. Critical control of lamp voltage to maintain a constant filament temperature is important.

The development of a quantitative oximeter is, of necessity, a long range program. Construction of improved miniature components for the earpiece providing the ideal spectral characteristics is a project in itself. Progress has been made in the electronic calculating circuit to permit the recording of the saturation value representing the ratio of (log R_0—log R_n) to (log IR_0—log IR_n). Finally, extensive and time-consuming calibrations must be performed to determine the limits of accuracy of a new oximeter.

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Discussion.—Dr. John H. Gibbon, Jr., Philadelphia, Pa.: I assume that a good many of you, like myself, have felt a little at a loss concerning some of these curves of the wave length of light. However, I think the work that Dr. Elam has done is very valuable.

We have been trying to improve upon the Millikan oximeter, which is now available. Dr. Miller, of our department, has constructed an oximeter which differs from the Millikan and which we think is better. We have used this instrument in some 20 intrathoracic operations. Because the patients are breathing a mixture of pure ether and oxygen, we find that their blood is completely saturated with oxygen during the course of the operation, and we find the instrument of little clinical value except in the induction phase of the anesthesia when the saturation may drop off and also in the immediate postoperative period when the anesthesia is discontinued.

Thus, immediately preceding the anesthetic and in the immediate post-anesthetic phase, I think the oximeter, particularly these improved models which Elam and others may develop, may be of considerable importance.

I hope they will be able to develop one which gives a linear deflection of the writing point with changes in saturation, instead of a larger deflection of the writing point as the upper limits of saturation are reached.

I assume Dr. Elam has checked the plateau, observed when breathing helium, by a catheter introduced into the right auricle directly measuring the saturation of the mixed venous blood. I assume he did not have an opportunity to tell us about that.

Another difficulty which we have encountered in the use of the oximeter has been that deflections occur when the patient's position is shifted on the operating table. When a patient is shifted from the horizontal to the head-down position a considerable deflection of the writing point occurs, which is unfortunate.

If we could develop an instrument which would continuously record the CO_2 tension of the arterial blood, we would have something much more valuable. Unfortunately, the physicists don't seem to be able to produce such an instrument.

DR. JAMES O. ELAM, St. Louis, Mo.: A linear oximeter scale would be more convenient for accurate reading, particularly in the lower saturation range. The alinearity of the Millikan compensating circuit oximeter is a result of taking a simple difference between the red and infrared transmission values. This relationship gives a range from 90 to 100 per cent saturation, which is approximately three times that between 50 and 60 per cent saturation. An electronic circuit for computing the logarithms of the red and infrared values and then taking their ratio would probably provide a scale for the oximeter that would be linear. This complex circuit may not be practical for general clinical use. Recently we have obtained evidence that a simplified circuit might be useful in providing an oximeter scale which is approximately linear.

Right heart catheterization studies to confirm the validity of the oximeter value for the mixed venous blood have been postponed until the accuracy of the oximeter would make such an evaluation worthwhile. Dr. Earl Wood of the Mayo Clinic has obtained evidence that the ear oximeter value during the "plateau" of the cardiac output determination is duplicated by measurements made simultaneously with a whole blood oximeter coupled to the radial artery. This method is theoretically valid only when a definite plateau is recorded within one circulation time following the inspiration of helium. When this does occur, one must assume that mixed venous blood is perfusing the lungs without change in oxygen content.

We have also observed the oximeter responses to changes in posture to which Dr. Gibbon referred. With the Millikan instrument these effects may be artifacts due to slippage of the earpiece or to actual changes in the amount of venous blood in the ear at the site of measurement. In severe cardiac patients such responses may be real. With our present technic, in which histamine is used to arterialize the ear blood, changes in posture of normal subjects does not produce these oximeter responses. It should be possible with the improved oximeters now in development, to interpret these effects, when they are observed in patients, with greater assurance that one is not dealing with instrumental artifacts.

THE EXPERIMENTAL STUDY OF FLASH-BURNS*

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THE WEAPONS OF MODERN WARFARE have produced a thermal lesion from a very brief exposure to radiant heat of high intensity that has been called a "flash burn." This was first encountered in a mass form during the bombing of Pearl Harbor in December 1941.[22] Eckert and Mader,[6] writing of the casualties from this say "only exposed surfaces were burned, even an undershirt or shorts appeared sufficient to prevent areas covered from being burned." No third degree burns were seen. The armed forces continued to encounter the flash burn throughout the war, but it was not until the Japanese casualties of the atomic bomb explosions at Hiroshima and Nagasaki were studied that the tremendous implications of the problem became apparent. Burns of all degrees of severity were observed there.

LeRoy[15] estimated that of the atomic bomb casualties in Japan 65 to 85 per cent were burned, 70 per cent sustained wounds, and over 30 per cent had irradiation injury. Others have estimated that over three-fourths of the casualties were from mechanical or thermal injuries. Those near the center of the explosion were, to use the words of Parsons,[21] "killed three times" by blast, heat, and irradiation. But the injurious effects of the blast and heat extended beyond that of the irradiation, hence the larger number of casualties which they created. The heat producing these burns was tremendous, and some individuals 2.5 miles (3 Km.) from the center of the explosion were sufficiently burned to require treatment. The sequelae were many and prolonged[15] and the incidence of keloids was high.[2]

The physical mechanism producing these high intensity burns is quite unlike that causing the ordinary burn seen in civil life. It is reasonable to suppose that its effect upon the organism will also differ, and that the local lesion, clinical course, and prognosis will not be the same. A thorough search of past literature, a survey of work done under OSRD contracts, a review of current work on burns, and personal inquiry, indicate that this problem has not received adequate attention, either from a basic or clinical standpoint. The clinical problem of the management of thousands of severely burned casualties is enormous. We have recently seen how a few hundred burn cases strained the medical facilities of Hartford or Boston. Imagine this situation multiplied 200 times! Obviously, the methods used in present practice are too

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elaborate, for they would have required at Hiroshima trained medical personnel in excess of the population of New Haven; materials and supplies greater than the gross tonnage of a Liberty Ship; and tank cars of blood. In the solution of this baffling clinical problem it appears obligatory first to know the characteristics and effects of "flash burns." What do they do to the skin? How do they affect the organism, and how can this effect be modified? What is their clinical course and how can it be altered by treatment? How lethal are they and what factors influence their mortality? To try to answer these and other questions one must produce and study the lesion experimentally. This report deals with laboratory methods of creating "flash burns" and the lesions produced.

REVIEW

Experimental burns have been produced by many individuals in as many different ways. Leach, Peters and Rossiter[14] caused a very satisfactory experimental, moderate temperature burn, using a vessel through which water of a known temperature circulated. They found that an application of 70 to 80° C of only 10 to 20 seconds duration produced severe "scabbing." Intervening temperature and exposure times produced roughly proportional injury. Microscopic examination of the tissues showed degrees of cellular disintegration, with mild burns and heat coagulation with the more intense ones. Among other conclusions they found that severity of the burn was dependent on the *duration* and the *intensity* of the stimulus.

In amplification of this work, Mendelsohn and Rossiter[17] made subcutaneous temperature determinations, using a copper-constantan thermocouple. They found that a rather prolonged exposure of 45 to 60° C was required to elevate the subcutaneous temperature. The temperature rose rapidly in the first two minutes, then levelled off gradually at four minutes, dropping slowly after the discontinuance of the burning iron application to nearly a normal range in the next six minutes. They made an excellent histopathologic study of cutaneous thermal injury in the guinea pig.

Working along the same lines, but with more adaptable equipment, Henriques and Moritz[12] sought to define the physical factors determining the transfer of heat energy through the skin. It was found that the caloric up-take rate of the skin, as measured by thermocouples at the dermis-fat interface, during the first 0.2 minute was about six-fold greater than the average caloric up-take during the ensuing 7 to 10 minutes. Maintenance of the skin surface for five minutes at 45° C resulted in heat saturation of the dermis. However, with skin surface temperatures of 50 to 70° C, edema fluid accumulated at the dermis-fat interface, thus cooling the dermis within and decreasing the effective thermal conductivity by some 15 per cent. The epidermis, it was calculated, became heat saturated within 0.5 to 1.0 minutes heat exposure, when brought immediately to the desired temperature at the surface.

The further establishment of the importance of *time-temperature* relationship was developed in the comparative study of burns on human and pig

skin. Using transepidermal necrosis as an end point, it was found that 44° C for six hours would produce an effect similar to 51° C for two to six minutes. When the surface temperature was lower than 44° C, there was a rapid decrease in the rate at which burning occurred, and the time-temperature curve was found to be asymptotic in the direction of the time axis. However, when the surface temperature was greater than 51° C, the exposure time was so short that during most or all of it the deeper layers were in the process of being brought to, rather than being maintained at, a state of thermal equilibrium with the surface. Thus the time-temperature curve above 51° C was found to be asymptotic in the direction of the temperature axis.

Moritz[18] in studying the pathogenesis of cutaneous burns, concluded that the quantitative results of a short exposure of high intensity might be similar to those of a long exposure of low intensity. However there were likely to be qualitative differences. Hyperthermia of high intensity resulted in a coagulative type of necrosis, in which the dead tissue was not autolyzed but rather disposed of by sequestration, while that of low intensity resulted in a noncoagulative type of necrosis, the dead tissue being autolyzed and readily susceptible to organization. It was possible, by using intense exposures of around 0.5 second duration, to carbonize the superficial shreds of stratum corneum without causing sufficient subsurface rise in temperature to damage the basal layers of epithelial cells, or to cause perceptible vascular reaction. Again, protracted vascular reactions were noted, without noticeable harm to the epidermis.

The findings of Henriques, Moritz *et al* are fundamental for any study of thermal injury. The demonstration of the time-temperature relationship and its importance in the production of different types of burns, forms a foundation for the further study of these types of burns. The observation was made that so brief an exposure to flame temperature is required to raise the epidermal-dermal junction to "cell-killing" level, that anything capable of impeding heat transfer to the skin, "would be sufficient to make the difference between burning and absence thereof." Even a thin film of moisture on the surface of the skin would be sufficient to prevent a burn at near threshold levels.[18] The continuation of this investigation will in effect be the extension of the curve (Fig. 1) towards the time axis, and away from the temperature axis.

METHODS

A flash source must have the characteristics to produce burns, and yet be controllable, and accurately measurable. It seemed that at least the following criteria should be met to produce an ideal flash:

1. Transient duration on the order of 0.1 second.
2. Extremely high intensity, of a known and possibly variable nature.
3. A known or obtainable spectral distribution.
4. Safety and convenience of handling.

The complicated nature of heat transmission makes it more practical to produce the burn by radiant heat. This also simulates field conditions. So attempts have been made to eliminate flame, or direct contact sources, *per se*. By confining the heat transmission to radiation alone, an accurate knowledge of the spectral distribution of the source is required, as well as its emissivity in its flashing state. Since the skin can be considered as behaving in the same manner as a perfect black body at 300°K,[10] absorption of radiations from such a source can be considered to be complete.

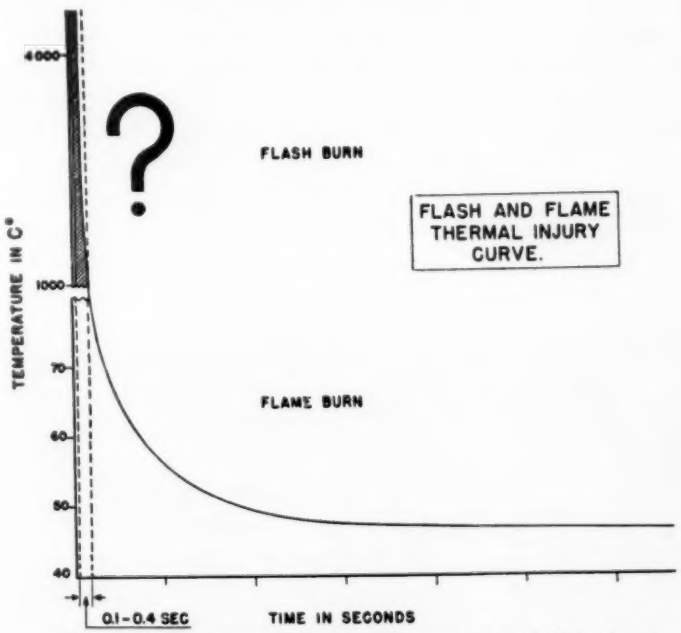

FIG. 1.—The curve of time-temperature thresholds of epidermal injury has been drawn from Henriques' results to include the "flash burn" range which is under investigation. Physical measurements in this area are difficult, but in general the experimental data obtained confirms that derived from computation.

Accordingly, a search for possible sources was begun. The agents tried are listed in Table I. Measurements of the duration, intensity and spectra of the various agents were gathered largely from the literature. Measurements under the experimental conditions are being made. Three general principles were tried: (a) the release of electrical energy from a bank of condensers to create a flash, (b) the creation of a constant high intensity source which is directed upon the target for known intervals by means of a shutter or trip mechanism, and (c) the use of substances that burn rapidly with an intense flame. (See Table I).

Anderson in 1919[1] described a method of exploding or burning a copper wire placed between two electrodes which were connected to a bank of condensers. Edgerton[7] used a similar arrangement for testing xenon photo-

TABLE I.—*A Summary of Various Sources, Their Physical Characteristics, Effectiveness, and Complications*

Source	Duration Seconds	Approximate Temperature C.	Burn Produced	Complication
(FT14) Electric discharge (xenon filled) Flash tube[7]	0.002	6300	None	Unable to focus energy
Exploding wire[1]	0.00001	20,000	None	Unable to focus energy Too brief Blast wave
Thermite[5]	Variable	3500	Not tried	Spatter Low intensity Handling difficulty
Gun powder[9]	To 1.0	3000	Failed	Low intensity radiation
Magnesium[28]	0.36	3500	Severe	Smoke
Carbon arc[18]	Constant	4000	Severe (Constant)	Small area burn

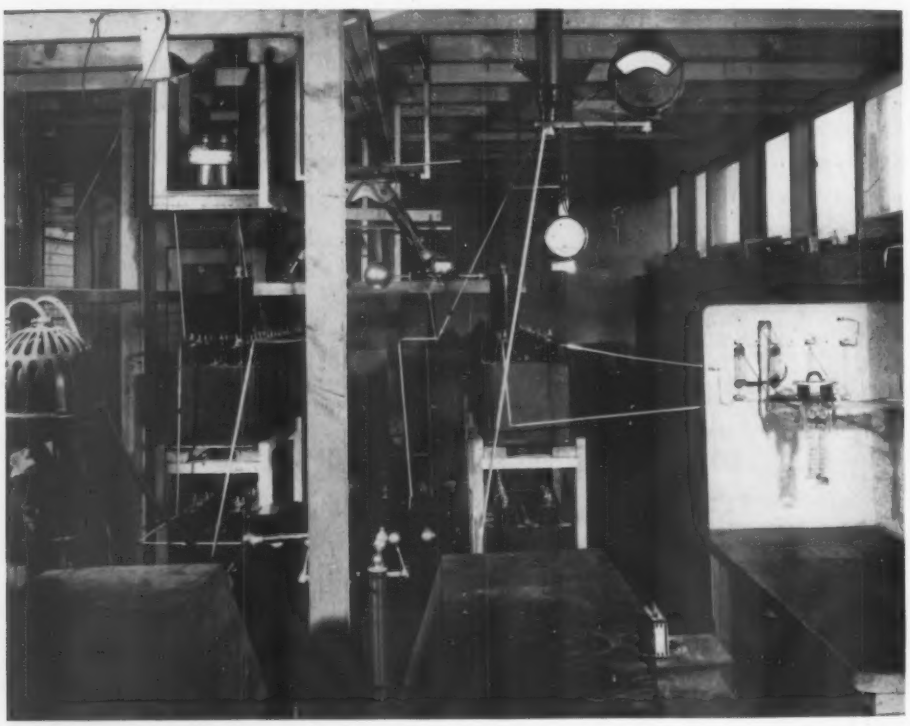

FIG. 2.—The bank of condensers is connected to the xenon filled flash tube (F. T. 14) of Edgerton. This method did not cause burning.

graphic flash tubes. Our condensers had a capacity of 64 microfarads and were charged to 25,000 volts (Fig. 2). Neither of these methods caused burning. The exploding wire generates temperatures in the range of 15,000 to 20,000° C, but this is so transient, in the order of 0.00001 sec., that injury does not occur. The inability to focus this energy and the blast wave produced are additional disadvantages. The Edgerton xenon filled flash tube produces approximately 6300° C in 0.002 sec. with 10,000 volts at about 16 microfarads. Efforts to magnify this by using 20,000 volts with 32 microfarads resulted in blowing out the flash tube. Burning by an electrical arc jumping across a gap was not tried. Flash burns are occasionally caused by means of an arc in the electric power industry but the intensities are greater than those produced in the laboratory.

Archimedes, by burning the fleet of Marcellus,[4] demonstrated the possibility of focusing heat with a concave reflector. Using this principle, the energy from a carbon arc source could be brought to a focal point and the intensity, here 4000° C, largely reproduced.* A timing device must then be added to the apparatus to limit the exposure. We have used a rotary type shutter as shown in Figure 6, or a car carrying the animal across the focal point at a known rate. The former method gives a "spot" burn whereas the latter results in a strip of burned skin across the side of the animal. This is a relatively precise method, capable of being controlled, which is very useful in observing the local changes produced but has the disadvantage of injuring only a relatively small area of the total body surface.

A variety of substances that burn quickly with a hot flame were considered, of which gun powder, thermite, 100 octane gasoline and magnesium were studied. The assistance of the Ordnance branch of the Department of the Army was sought, and several arsenals were visited. Plants of the photographic industry, and the electrical industry dealing with illumination were also visited. To date, magnesium has been found to be the best source of this type. It is much more easily controlled and handled than others, gives a high intensity in a short time and has as its only disadvantage the production of smoke. We have detonated as much as three pounds of magnesium powder without disaster. A contrasting example is thermite, which causes extreme spatter of hot particles (Fig. 3), giving contact burns that confuse the experiment. It is also dangerous and difficult to handle.

Fauley and Ivy[8] devised a small brass cannon, which would spark fire aliquots of 0.5 Gm. of magnesium at "targets," such as filter paper, rabbit skin, and the forearms of human subjects. At a distance of 24 cm. from the maw of the cannon the temperature was estimated at 1,000 to 1,500° C, while at the mouth of the device it was about 2,600° C. An undershirt served to protect the skin against the burn, and an ointment of 50 per cent titanium dioxide prevented the flash burn.

We used a standard photographic flash powder, practically pure mag-

* We are indebted to Dr. Rudolph Langer for assistance with this apparatus.

FIG. 3

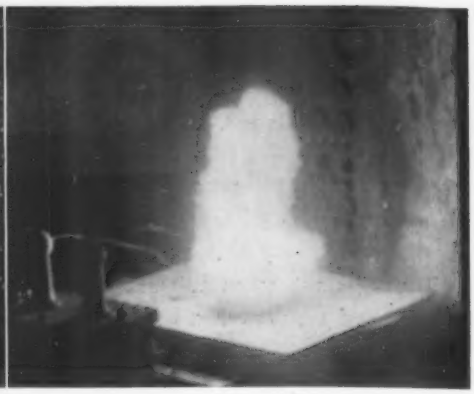

FIG. 4

FIG. 3.—Burning thermite, with or without magnesium added, results in widespread dissemination of molten iron particles which complicate the experiment by contact burns. Thermite is also difficult and dangerous to handle, has a relatively slow rate of combustion and is not a suitable source for producing flash burns.

FIG. 4.—The early stage (about 1/30 sec.) of burning magnesium showing the shape of the flame. The transformer igniter and shielded box containing the anesthetized experimental animal are also shown.

nesium. Various methods of firing were tried, the most dependable being a high tension electric spark resulting from 110 v, 60 cycle A.C. current being passed through a GE type K 916 x-ray transformer, connected in series with a resistance coil used as a ballast. It was necessary to do most of the firing in the open, because of the large amount of smoke generated by the combustion of the agent.

FIG. 5.—A later stage of burning magnesium which demonstrates the size of the flame and the smoke produced. Magnesium is a satisfactory source to produce flash burns.

High speed motion pictures were taken of the flash, from which the duration was computed. For 124 Gm. the flash duration was about 0.338 second (Figs. 4 and 5). From these same films it was found that when the magnesium was burned on a flat surface of fire-resistant material, the flame and flash seemed to spread diffusely in a hemisphere about the source. However, when it was placed in a saucepan, with upward sloping walls, the flame was seen to go up at an angle corresponding to the angle of the pan edge.

Preliminary studies of the flash duration made with a phototube pick-up device recorded on a cathode-ray oscilloscope, paralleled the motion picture findings. Radiation

calorimetric studies, using various black-body receptors as well as indicators, are in the phase of development.

From the work of Moritz, *et al*[20] the swine was shown to have a skin very similar in structure and physiologic reaction to that of the human being. Therefore, the pig was chosen as the standard experimental animal, though some experiments have been done on dogs, rats and rabbits. Young Chester white pigs were chosen, about two months old, with weights of 8 to15

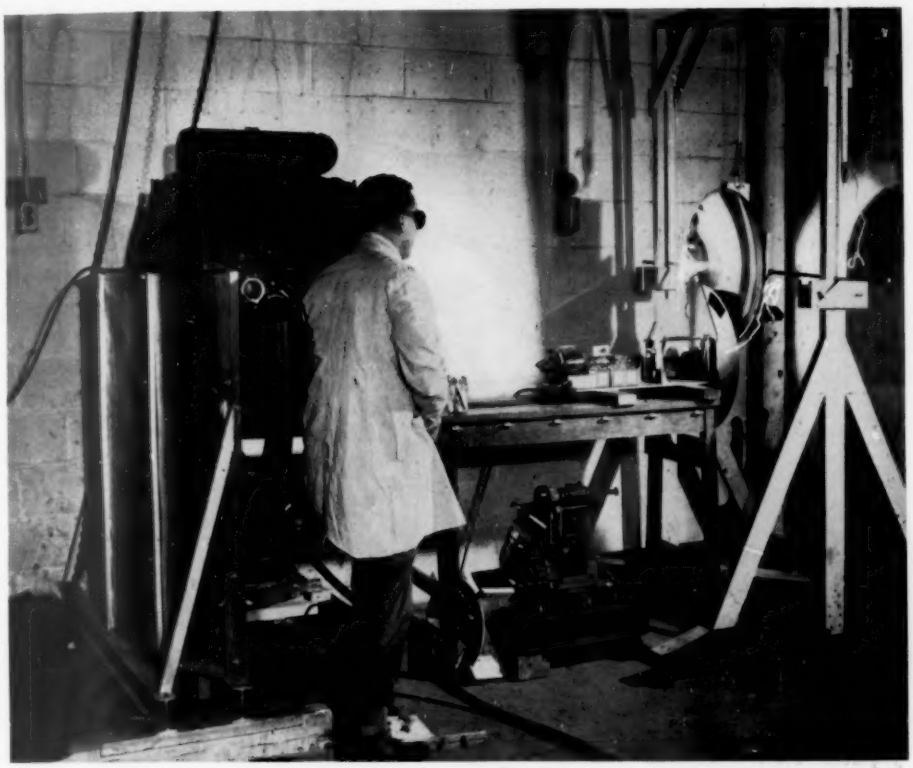

FIG. 6.—A 24-inch Army carbon arc searchlight is directed at a concave reflector which brings the focal point into the range of a high speed, electrically controlled, flash producing shutter. A car can also be used to traverse the focal point at a known rate.

Kg. These were well anesthetized with veterinary nembutal given intraperitoneally, or intravenously into the superior vena cava.[3] One side of the animal was closely clipped. The clipped animals were placed in a box, one side of which contained perforations. Through these perforations a variable area of the lateral surface of the pig was exposed. This surface contained skin of approximately the same thickness, and was fairly smooth. The distance and the amount of magnesium were varied at first but later a standard experiment was set up in which 124 Gm. of magnesium was used with the box at 30 cm. from the source.

Immediately after the flash the burns were observed, measured and photographed with 35 mm. Kodachrome, panchromatic, or infra-red film. The areas were biopsied at various periods of time, ranging from one hour to two weeks; special emphasis being placed on the 1, 6, 12, 24, 48, and 72 hour periods. Usually no more than one biopsy was taken from each burn and it was so taken as to include a generous portion of normal skin on either side. The sections were fixed in Bouins solution and stained with hematoxylin and eosin. Ninety burns have been studied in this way.

The burns received no treatment. The animals were kept on their diets of commercial pig feed throughout. If one died as a result of anesthesia (which was often the case early in the work), a complete autopsy was done, including histologic examination of all burned areas.

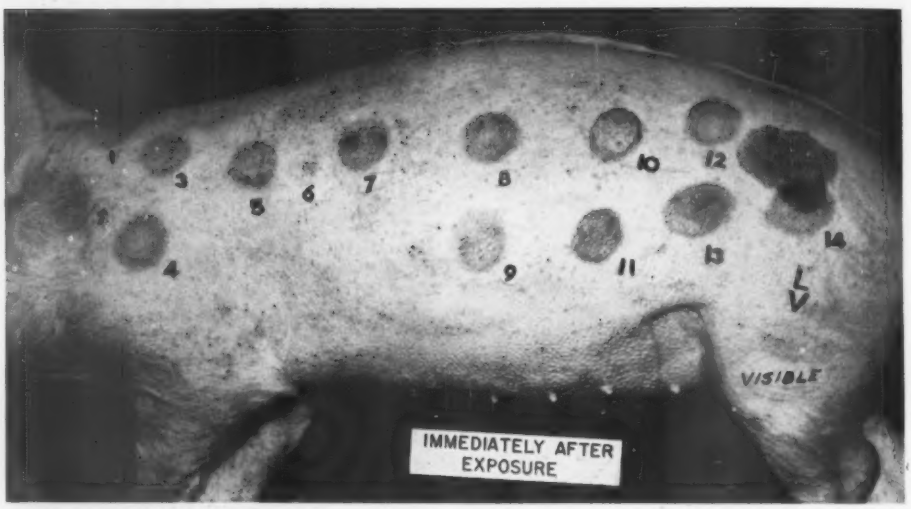

FIG. 7.—Small circular burns produced immediately after exposure to 124 Gm. of burning magnesium at 30 cm. These occur through 3.5 cm. holes bored in the side of the animal box.

RESULTS

Theoretically, the rapid exposure to intense radiant heat should change the histologic picture, for there is not time for reflex vasodilitation from warming nor from the axone reflex. This prevents the cooling effect of blood in dilated capillaries. The rapidity of the injury should not allow lateral diffusion of heat, so making the margins abrupt. This same speed might also prevent the cooling at the dermis-fat interface, thus allowing deeper penetration. In general these theoretical considerations were confirmed by observation.

The severity of the burns produced varied with the distance of the skin from the source, the amount of energy used, and the anatomical location of the burn area. In the pig the mild lesions were characterized by an erythema

which developed within the first few hours, deepening in color, and becoming tan or brown over the next few days, and finally disappearing within a week with perhaps a fine scaling of the surface.

The moderately severe lesions demonstrate a peripheral flare. This flare subsides within one hour, leaving a ring of erythema about a central gray-white area of dry, cutaneous necrosis. The erythema again deepens in color, subsiding within a week. The central area also deepens in color and becomes thickened and raised by 24 hours. The edema reaches its peak by 48 hours,

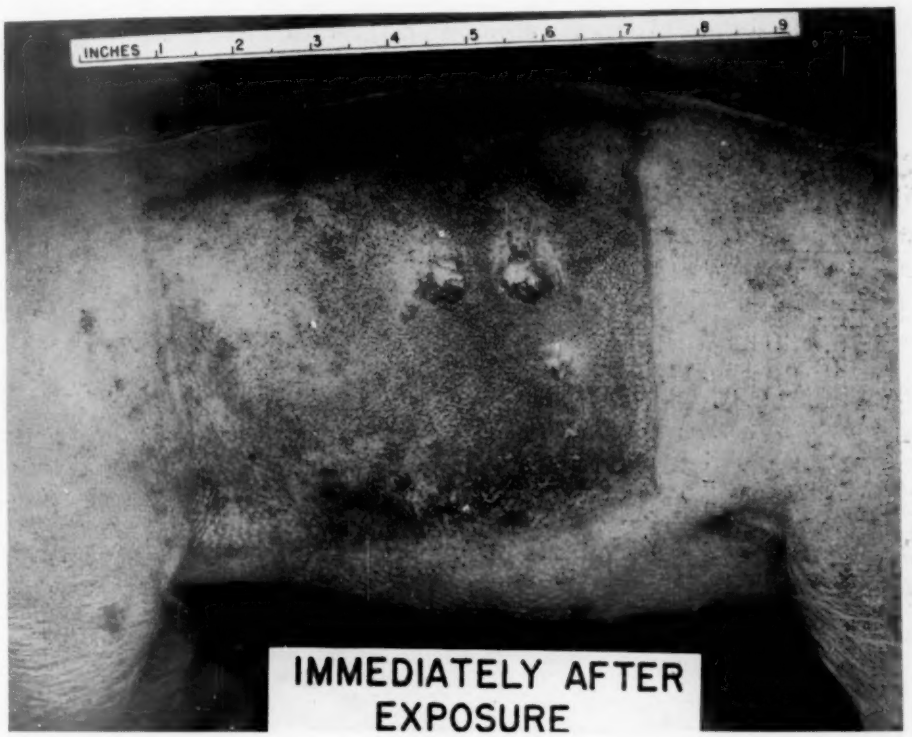

FIG. 8.—A burn 10.5 x 15.0 cm. in size produced through a larger port in the animal box by burning 124 Gm. of magnesium at 30 cm. distance.

then subsides, giving way to induration and later to a flat, brown crust covering the burn (Figs. 7 and 8). The crust remains adherent to hairs which have grown out, but it finally drops off in seven to ten days. Occasionally, vesicles are present in the central necrotic area immediately after the burn, or the epidermis may be separated entirely, leaving a raw dermal surface exposed.

Histologically, the flash burn presents several interesting features not noted in the moderate temperature burn. The common type (moderately severe, produced by 124 Gm. of magnesium burned at 30 cm. from the skin) presents a shredded stratum corneum. The epidermal transition from

burned to normal epithelium is abrupt (Fig. 9) and often accompanied by epidermal-dermal separation at the line of juncture. The unburned epidermis is basophilic, the cells of normal architecture (Fig. 10), and immediately adjacent, the burned cells are eosinophilic, present nuclear pyknosis and cytoplasmic vacuolation. The burned cells run the gamut of types described by Leach, Peters and Rossiter. Various degrees of dermal-epidermal separation are present throughout, with attachment by elongated tono-fibrils in some areas. A similar abrupt demarcation of burned from normal epithelium is seen in the skin crypts and the hair follicles with deeper injury. The dermis reflects the depth of the penetration by a coagulation of the fibrils, with some fragmentation appearing later. These changes are less striking, and so are harder to detect.

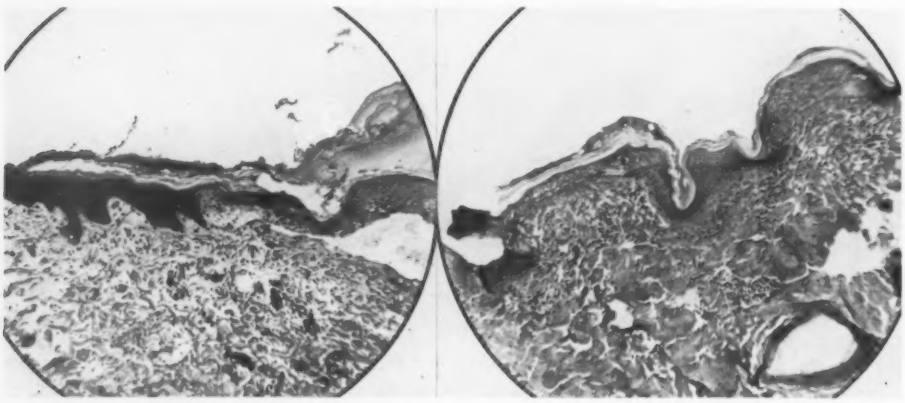

FIG. 9 FIG. 10

FIG. 9.—Biopsy immediately after burning which shows the abrupt lateral delineation of the injured epidermis and epidermal-dermal detachment x 65.

FIG. 10.—Biopsy 12 hours after exposure showing sharp horizontal demarcation through a hair follicle and mild upper dermal coagulation x 65.

In the sections, the edema is manifested by a loosening of the dermal collagen fibrils, this appearing about six hours after burning. Polymorphonuclear leukocytic infiltration appears simultaneously. By 24 to 48 hours, both phenomena are at a maximum, fading off thereafter, to disappear entirely in the milder lesion by the fifth day.

Healing is fairly rapid in the pig in the mild and moderately severe burns. Re-epithelialization begins at 48 hours and generates from surviving epithelium of hair follicles, crypts and lateral margins. It is completed by ten days. The thermally damaged epithelium is undercut by the growing epithelium and the former shed as a dense sequestrum. This eschar remains, covering the lesion, several days after complete re-epithelialization has occurred. Only rarely was granulation seen in the experiments.

In the more severe, transcutaneous burns, demarcation is not as marked laterally or in depth. The epidermis, dermis and underlying fat have a fixed, coagulated appearance. The characteristic leukocytic boundary and healing

by granulation seen in lower temperature burns are present in this degree of flash burn. It is our impression that if the injury penetrates deeply, its horizontal nature may destroy all epithelium in crypts and hair follicles, leaving no epithelial islands for regeneration.

DISCUSSION

The severity of the flash burn is a rough index of the intensity of the burning stimulus, and as such, is governed by the laws of energy transfer. Severity varies inversely as the square of the distance of the skin surface from the source. It varies also with the intensity of the source, the thickness of the skin and with the curvature of the cutaneous target exposed to the source.

The most striking characteristics of experimental flash burns are found in the histologic picture. Most remarkable is the abrupt and diagrammatic demarcation between burned and normal skin. The normal, basophilic epidermal cells change, on a straight line, to the acidophilic burned cells which have all the characteristics of thermal injury. In the deeper skin this demarcation is at the burn border, in the crypts and hair follicles. It is present in the dermis but is less easily demonstrated. There is no gradual transition zone from normal cells to burn cells as described by Leach, Peters and Rossiter, and Moritz in the moderate temperature, long duration burns. Moritz[19] noted the phenomenon of demarcation on a few occasions when his animals were subjected to high temperatures for brief exposures.

Another characteristic of the flash burn is the method of healing. The burned epithelium and dermis represents a coagulative "fixed" type of necrosis, with eschar formation and subsequent sequestration, rather than the organization in the non-coagulative necrotic tissue of the moderate temperature burn. With a flash burn of average severity the epithelium grows out freely (and indeed beautifully) from normal borders and hair follicles, beneath the unorganized eschar, so that healing is rapid. Yet if the area is large and the injury deep enough to destroy the epithelium in the crypts and hair follicles, then this characteristic of demarcation will result in delayed repair from lack of epithelial islands.

The demarcation seen is probably a function of the rapid transcutaneous heat transfer. This process is most difficult to measure. It is relatively easy to compute the energy of the source, but much harder to record that delivered on the target. Physicists have told us it is practically impossible to measure the penetration of that energy into the skin. The transfer is so brief that the lag in ordinary instruments prevents recording. Yet it is felt that efforts should be continued to measure the heat penetration at various levels, for it is desirable in an understanding of the physiologic and pathologic changes created. Some of the work done on burns in the past is difficult to evaluate because of the lack of such precise physical measurements.

The studies on the effect of flash burns are being continued. This report is limited to the lesion produced in pig skin. The observations on the histo-

pathology and healing of severe trans-dermal burns are incomplete and are being extended.[13] The influence on the healing process of anemia, infection, hypoprotenemia and ionizing irradiation will be studied. There is much that remains to be done. Yet at present we feel that the short exposure of high intensity heat causes differences, both histologic and reparative, from those seen in moderate temperature burns. Whether or not this will alter the systemic effect of the burn on the organisms remains to be seen.

SUMMARY

1. Methods are described which produce a short exposure of high intensity radiant heat capable of creating a flash burn.

2. Observations on the gross and histologic changes in the skin of pigs injured by flash burns indicate that the lesion is dissimilar from the ordinary moderate intensity burn.

3. The healing process in flash burns is not the same as that in moderate temperature burns.

4. It is felt that the differences noted are intimately related to the physical transfer of heat through the cutaneous layers.

5. It is planned to extend these observations to study of the many variables which may alter not only the local changes but also the systemic effects.

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Discussion.—Dr. Everett Idris Evans, Richmond, Va.: The paper by Dr. Pearse and his associates is timely and important. The importance lies in the fact that he has developed a method which produces a flash burn which in many ways simulates the burn caused by explosion of an atomic bomb, that is, a burn caused by a vast burst of energy of very short duration but enormous intensity.

The local pathologic effects on the skin appear to be different than heat of lower degree, but it remains for future study to determine how much and in what sense are altered the metabolic effects by this particular type of thermal injury.

(Slide) You can see from this slide that radiation injury accounted for not much more than 15 per cent of the casualties at Hiroshima.

The chief importance of Dr. Pearse's presentation to this surgical group may be that he has placed in a proper light, I think, the true nature of the atomic bomb effects on civilian and military personnel.

As far as recent publications and public discussions show, the chief interest, medically speaking, in the new bomb has been the radiation hazard. This may be true because to most of us this hazard is bizarre and mysterious. We fear most what we understand the least. I would be the last to deprecate the radiation hazard imposed by this new bomb, but even superficial analysis of the lethal effects of its use at Hiroshima and Nagasaki will show that a greater number of persons died from thermal injury than from radiation injury.

The surgical significance of this fact has not been stressed properly. It is important because it is in the group of persons suffering from major thermal but minor radiation injury (that is, outside the two kilometer zone) that most of the salvageable will be found, if proper research and proper preparation is made for the care of these casualties.

What does this proper research and proper preparation entail? This is mentioned here because, as Dr. Rankin stated in his presidential address, it is mainly on the membership of this organization that the responsibility will fall for this research and development.

As a nation we need at once constructive efforts which will lead to the solution of some of these problems; I state here some of the more important as I observed them at Hiroshima and Nagasaki:

First, a better understanding of the pathologic physiology of the seriously burned patient as regards the shock period, renal and liver damage, and especially, in some cases of secondary burns, pulmonary complications.

Second, a useful plasma substitute such as gelatin, polyoxygelation, or the new dextran, obtainable in large quantities. To my mind, it is simply foolish to think that we will ever have plasma or whole blood in the necessary amounts.

Third, better physical and chemical methods for the long storage of whole blood, and knowledge of the physiological effects of massive infusions of whole blood. We know practically nothing of this latter matter.

Fourth, practical methods for the simplest treatment of mass burn casualties, chiefly involving face and hands.

Fifth, a better treatment of burns complicated by other forms of trauma.

Sixth, better treatment of burns complicated by infection in states where the ordinary bone marrow response is hampered by minor radiation damage.

These problems are solvable if as a group we put our shoulders to the wheel. Our responsibilities as citizens and surgeons demand this. Ordinarily we like to think of the atomic bomb as affecting only enemy populations. It may be well for us to remember the admonition of Dr. Samuel Johnson, "Think not the doom of man reversed for thee."

DR. ROBERT ELMAN, St. Louis, Mo.: Gentlemen, it seems to me that Dr. Pearse's observations have an application to present problems of burns which we see in civilian life. He has called attention to the fact that the kind of burn and its systemic manifestations should really be defined in terms of the kind of stimulus, that is, the temperature and duration of the thermal agent.

Many years ago, in some unpublished observations, we showed that one of these systemic infections, namely, hemo-concentration, is influenced by, but not necessarily in direct proportion to, the stimulus. In other words, very often we would find greater degrees of hemoconcentration with lower temperatures or with a longer duration of the thermal stimulus. Indeed, we were led to the observation that quite apart from the usual three degrees of burns described in textbooks, a burn may produce three types of tissue damage:

First is the simple edema without necrosis, which leads in general to loss of plasma and hemoconcentration without toxic or other systemic manifestations. Second, the dry hard necrosis which leads to neither hemoconcentration nor systemic manifestation. Finally, the wet necrosis, which may lead to both.

Dr. Pearse's photographs showed that many of these flash burns seemed to produce a thin layer of dry necrosis. I would like to ask whether in any of his other observations simple edema without necrosis, or moist necrosis, was produced.

DR. CHARLES C. LUND, Boston, Mass.: I want to discuss for a moment one phase of the subject that Dr. Pearse took up so ably.

He mentioned that the occurrence of the numerous casualties in the Boston and Hartford fires strained the available medical facilities. What would it have been if it had been 200 times worse? He is absolutely right in those statements.

At the Massachusetts General Hospital there were quite a large number of very competent men, well trained in the most modern treatment of burns, and that treatment was carried out very satisfactorily. Over at the Boston City Hospital we had three times as many cases. Our studies of burns were of much shorter duration than those at the Massachusetts General, and the small staff that had been studying burns had to spend most of its time in directing the treatment of shock and other acute problems.

The doctors at the hospital made no attempt, in more than two or three cases, to carry out the complicated pressure dressing of the burns. The hospital staff reverted to

the previous standard treatment of triple dye, for which the hospital had plenty of supplies and plenty of knowledge as to how to do that treatment well.

When Hartford's fire came some of the patients were taken to the Hartford Hospital, which was well equipped and which cared for their patients with the most modern treatment. However, a very large number of patients were taken to a rather small hospital where there had been no particular interest in burns and where treatment was carried out by varied specialists, many of whom were not surgeons. That particular hospital had a resident staff of only two young men, and staff men did most of the work.

Someone, unfortunately, told them that Levenson and I had had published a paper on the plaster cast treatment of burns, and that the plaster cast treatment of burns was what should be done for those patients with burns of the extremities. The result was that the casts were put on by people who did not understand the physiology of that treatment, and most of the casts had to be taken off within 24 hours and other treatment given. There was real harm to some of the patients from the cast treatment.

All of this leads up to a plea for the simplest possible effective measures to be encouraged for the doctors and the population to carry out, rather than complicated methods. If it is a question between a doctor or a person carrying out an ideal method that he does not know very well, I think it is good judgment to use a slightly inferior method that he does know.

DR. HERMAN E. PEARSE, Rochester, N. Y.: I would like to thank Doctor Evans, Doctor Elman and Doctor Lund for their discussion. I will try to answer Doctor Elman's question. We have worked on the pig, which is very resistant to infection. The lesions produced thus far by a standard experiment of 120 Gm. of magnesium at 30 cm. distance did not become moist burns, but were covered with a dry eschar. The greater intensity deeper burns or burns produced in other animals may become moist.

In conclusion, I would like to say that I was a little hesitant about presenting this subject before this group because it is so remote from your daily lives. I decided that there was no need of being apologetic about it, for if there is ever an atomic bombing in this country, we as surgeons must take care of the casualties. If we analyze the problem and study it, at least we will be prepared.

BLOOD STASIS IN THE LUNGS AS A FACTOR IN THE ETIOLOGY OF POSTOPERATIVE PULMONARY COMPLICATIONS*

HERBERT C. MAIER, M.D.

NEW YORK, N. Y.

KNOWLEDGE CONCERNING initiating factors is most important in understanding the development of pathologic states. Too often the secondary or later features of the morbid process obscure the initial aberration which set the train of events in motion. This applies to the pulmonary complications which follow abdominal and other operations. The important rôle of blood stasis within the lungs in initiating the process which later develops into atelectasis and pneumonia has not been adequately appreciated in spite of the excellent work of Drinker.[4] Comprehension of this fact leads to a more rational approach to the prevention of these complications.

It should be emphasized at this point that the etiology of postoperative pulmonary complications varies in different cases. Among the causes that may be listed are retained bronchial secretion, aspiration of foreign material into the tracheobronchial tree, pulmonary embolism and primary bacterial invasion. Although some of the most serious pulmonary complications may be due to the aforementioned causes, these cannot be evoked to explain the initiation of the process in the majority of cases. Hypoventilation is a factor of considerable importance, but the mechanism by which its deleterious effects are produced has not been completely clarified.

The importance of secretion in the bronchi in the development of pulmonary complications has been given much consideration in recent years. The significance of this factor is great. A logical explanation of the source of such secretions, however, has often been wanting. In some cases the presence of bronchial secretions can be explained on the basis of one of the following mechanisms: (1.) Response to irritating anesthetic vapors or mechanical irritation of the air passages; (2.) aspiration of material, such as saliva into the airway; and (3.) retention of secretion caused by pre-existing pulmonary and bronchial pathology. In most cases, however, none of the above explanations apply. An abnormal amount of fluid in the pulmonary tissues is here postulated as a frequent source of bronchial secretion. There are a number of ways in which the fluid content of the lung may be increased. These are: (1.) Circulatory stasis, (2.) hypoxia, (3.) cardiocirculatory failure, (4.) partial obstruction of the airway, (5.) general tissue changes which favor edema such as sodium retention, Vitamin C deficiency, hypoproteinemia, etc., (6.) chemical and physical irritants, and (7.) reduced ciliary action and lessened evaporation from the lungs associated with hypoventilation.

Circulatory stasis, which is usually not mentioned in a discussion of the etiology of postoperative pulmonary complications except in cardiac patients,

* Read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

is here deliberately placed at the head of the list, and is the subject considered in this paper. It is my belief that an alteration in pulmonary blood content is a factor of fundamental importance in the initiation of many postoperative pulmonary complications. Physiologists have long known that the lungs serve as a blood reservoir. The structure of the lung is well adapted to blood storage. Contrary to solid organs, such as the liver and spleen, which also act as blood reservoirs, the lungs can store a large amount of blood without any increase in external dimensions. The congested liver and spleen enlarge, whereas the congested lung may actually become smaller. The reason for the difference lies in the fact that the increased volume of blood in the lungs causes the engorged capillaries to encroach on the alveolar spaces and hence diminish the amount of gas contained in the alveoli. Diminution in vital capacity is used as an index of pulmonary vascular congestion.

Numerous studies have demonstrated the frequent alterations in blood flow and blood content which occur in various organs or parts of the body in response to physiologic demands. The magnitude of such fluctuations may be surprisingly great. Marked alterations can occur in a period of minutes. These vascular responses are due to various neurogenic, physical, chemical and hormonal factors. The relative importance of the controlling factors varies greatly from organ to organ. One must constantly bear in mind the difference between the volume of blood flow through an organ and the total blood content of that organ. The two values are not directly related. In the lungs, for example, the blood content is less when the rate and minute volume of blood flow is increased during exercise. Another very important factor, however, is the vascular status, and circulatory demands, of other parts of the body. DeBakey and associates[2] have referred to a "lending-borrowing" mechanism in the re-distribution of blood associated with pathologic states. In such a process the "bank" or reservoir is an important consideration. Since the lungs are one of the most important blood reservoirs in the body, the numerous factors which alter the amount of storage in the lungs deserve far greater consideration.

Hamilton and Morgan[6] showed that a change from the upright to the recumbent position reduces the vital capacity because of a redistribution of blood. The lungs serve as a storage place for the blood which drains out of the dependent veins on lying down. This conception is substantiated by the fact that when blood pressure cuffs are applied to the four extremities while the subject is upright, and blood is trapped in the arms and legs by raising the pressure in the cuffs to a diastolic level, there is no similar reduction in vital capacity on assuming the recumbent position. But the increased blood content of the lungs during recumbency and bodily inactivity is not evenly distributed. Because of the low pressure in the pulmonary veins, gravity has a greater influence on the pulmonary than on the systemic circulation. Position plays an important role in determining the distribution of the blood within the lungs, especially during hypoventilation. The anatomical relationship of the various parts of the lung to the site of the entrance of the pulmonary veins into the left

atrium is important. A greater pressure is necessary to drain the blood from the parts of the lungs which are below the level of the veins. Moreover, the portions of the lower lobes caudad and posterior to the level of the inferior pulmonary vein are known to be the usual site of postoperative complications.

Ventilatory motion plays an important role in pulmonary circulation. The more negative intrathoracic pressure associated with inspiration causes an increase in the amount of blood entering the right side of the heart and pulmonary circulation. The left ventricle then responds by also increasing its output. A remarkable adjustment keeps the output of both ventricles essentially the same except for transient changes. Otherwise, large fluctuations in the blood content of the lungs would constantly occur. Much additional data is needed concerning the mechanism by which this adjustment is attained. Only then can it be known whether different breathing patterns with variations in the relative length of the inspiratory and expiratory phase will influence significantly the tendency toward blood stasis in the lungs. The importance of mechanical movement in aiding pulmonary blood flow has been forcibly demonstrated by Thompson's experiments.[8] In heparinized freshly killed animals alternating positive and negative intrabronchial pressure caused movement of blood through the lungs after all heart action had ceased. It is a common clinical observation that definite improvement in the peripheral circulation of patients in the early postoperative period is noted when a few deep breaths are taken. What changes in the blood content of the lung are produced by such increased ventilation have not as yet been accurately determined.

The deleterious effects of hypoventilation in surgical patients have been widely recognized. The reduced ventilation has been ascribed to splinting of respirations due to pain, respiratory depression from drugs, and bodily inactivity. Blood stasis in the dependent portions of the lungs should be added to this list. Pulmonary congestion reduces the elasticity of the lung, with resultant hypoventilation and elevation of the diaphragm.

Drinker[5] has made extensive studies of the pulmonary changes produced in the dog by lying quietly under nembutal anesthesia for several hours. He demonstrated by means of an aerosol dye that the dependent congested parts of the lungs are very poorly ventilated. The reduced blood flow in the congested areas was proved by the distribution of intravenously injected graphite particles.[4] Drinker has also emphasized the contrast between the human being during normal sleep and the heavily sedated or postoperative patient. The respiratory amplitude and body activity are much less in the latter group. The occasional deep sigh and unconscious movements during ordinary sleep may well have a purpose.

Experimental studies have repeatedly demonstrated that infarction of the lung will not occur following embolic occlusion of a branch of the pulmonary artery unless pulmonary congestion is already present.[3] Since pulmonary infarction does occur in postoperative and inactive patients, circulatory stasis would appear to be present under these conditions. Also the frequent finding

of congestion in the bases of the lungs at autopsy when death occurs in the early postoperative period yields corroberative evidence. Moreover, pathologically it is often difficult to make a definite distinction between pulmonary congestion and pneumonia.

Since blood storage in the lungs is a factor in the causation of pulmonary complications, it might be expected that the incidence would be higher in those patients who normally have a larger amount of blood in their extremities, such as muscular males, which is transferred elsewhere during inactivity. The high incidence of pulmonary complications in cases of splenectomy, especially where there is marked splenomegaly, may be due to the removal of one blood reservoir which would tend to increase storage elsewhere. In general the total blood volume is not as important as the body blood distribution in influencing the blood content of the lung. The factors of primary importance are the extrapulmonary demand and the ability to empty any excess blood from the lungs.

In the day when the irritating effect of inhaled anesthetic vapors was considered the main factor in the subsequent development of pneumonia, it was anticipated that the introduction of spinal anesthesia would result in a marked reduction in the incidence of pulmonary complications. This fallacious assumption was due to misconceptions as to the initiating factors. The failure of spinal anesthesia to significantly change the incidence of postoperative pneumonia is readily understandable when it is realized that bronchial secretion may be due to blood stasis and hypoventilation.

Van Allen *et al*[9] have demonstrated the importance of collateral respiration through the intra-alveolar pores in the maintenance of pulmonary aeration in spite of bronchiolar obstruction. Inadequate recognition has been given to this important work. Alley and Lindskog[7] recently reported that the injection of histamine reduced or abolished collateral respiration through the intra-alveolar pores, and thought that histamine released in the operative area might be a factor in pulmonary complications. This does not seem likely, because the available evidence does not support the theory that significant amounts of histamine are released into the circulation during a properly performed operation. Moreover, pulmonary complications similar to those of the postoperative period are also seen in heavily sedated bedfast patients who have not undergone a surgical procedure.

Since bodily inactivity and depressed respirations are considered harmful factors tending to cause pneumonia, mention should be made of the Barach equalizing pressure chamber.[1] Patients may spend much time in such an apparatus in which there is relative immobility of the thorax and little movement of the rest of the body. Pneumonia has not resulted therefrom. In this chamber, however, the lungs are subjected to rhythmic pressure effects that may well affect the movement of blood in the lungs. Such patients also do not feel the usual urge to move other parts of their body, probably because of the circulatory effects of the rhythmic positive pressure to which the entire body is subjected.

The incidence of mild pulmonary complications has not been reduced in recent years as much as the frequency of the obvious postoperative pneumonia. Antibiotics and other improvements in postoperative care have lessened the frequency of clearly manifest pneumonias. Further attention should now be directed to the reduction of the milder complications by attempts to eliminate the initiating factors.

Prevention of pulmonary complications requires observance of the following:

1. Use anesthetic technics which do not
   (a.) depress respiration considerably
   (b.) produce even a slight degree of hypoxia
   (c.) cause labored breathing or undue resistance in the airway
   (d.) depress systemic circulation and thus favor blood storage in lungs.
2. Remove secretions early in the tracheobronchial tree.
3. Provide for good ventilation of all parts of lungs in the postoperative period.
4. Reduce pulmonary blood stasis by maintaining good blood flow in other parts of body.
5. Minimize pain that interferes with good pulmonary ventilation.
6. Obtain aid of gravity in draining parts of lung below the level of the pulmonary veins by turning patient periodically completely on the side or to a prone position.
7. Avoid hypotension because of unfavorable effect on blood distribution in the body.
8. Avoid abnormal increases in blood volume.

CONCLUSIONS

The muscular inactivity and depressed function of the surgical patient during and immediately after operation lessens the demand for blood in large portions of the body. A resultant accumulation of blood occurs therefore in some viscera. The lungs are an important blood reservoir. Because of the low pressure in the pulmonary venous system, position will play a significant role in determining the distribution of the blood accumulated in the lungs. Abnormal ventilatory motion and little change in body position over a period of some hours also play a role.

The blood stasis in the dependent part of the lungs is a factor which predisposes the postoperative patient to the development of atelectasis and pneumonia. More attention should be directed to the avoidance of pulmonary blood stasis since this is an important *initiating* factor. The lower incidence of postoperative pneumonia since the advent of chemotherapy does not mean that the process is primarily an infectious one in most instances. Prophylaxis of postoperative pneumonia depends largely on eliminating the factors that render the surgical patient more prone to a secondary bacterial invasion. Thus the undesirable sequence of events may be checked at its onset.

The author is keenly aware of the present lack of direct measurements of the blood content of the lungs in various physiologic and pathologic states. More investigation of circulatory alterations within the lungs of surgical patients is needed. In the future anesthetic technics should also be evaluated on the basis of their effect on the blood content in the lungs. Pulmonary blood stasis should be included in the list of etiologic factors in postoperative pulmonary complications. Although this paper has dealt with surgical cases, similar mechanisms are also present in the inactive, bedfast medical patient.

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ELLIPTICAL ANASTOMOSIS IN UROLOGIC SURGERY*

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SURGEONS WHO PERFORM operations upon the urogenital tract often find it necessary to transplant the ureter or the urethra from its natural location to some other site. And when procedures of this sort are carried out the results are often compromised or even defeated because of constriction at the site of anastomosis. The cause of constriction at these areas appears, in part, to be related to the small size of the normal ureter and urethra; but other factors undoubtedly play a role in the matter, since stricture formation is the rule rather than the exception in many situations.

Some notable examples are to be found in cutaneous ureterostomy, which is often performed for supravesical diversion of the urine; and perineal urethrostomy which is necessary when the penis is radically amputated for cancer. Most surgeons in performing these operations have brought out a long segment of the ureter or urethra and have carefully preserved the enveloping adventitia, hoping by these measures to preserve a viable nipple of tissue, projecting above the skin surface much like a well formed colostomy. But even under these conditions contraction often occurs, necessitating periodic dilations; and in some instances, continuous drainage with an indwelling catheter becomes necessary. Concentric constriction of the circular structures appears to be a handicap to normal patency in these cases, and this type of constrictive tendency has constituted a hazard to the successful outcome of these, as well as other plastic procedures upon the ureter and the urethra.

Various technics (Fig. 1) have been utilized in an effort to overcome this constrictive tendency. All of these technics have one feature in common: the direct suture of one epithelial border to another. But even when successful union has occurred following direct anastomosis, the inherent tendency to concentric constriction has often given rise to stricture at the point of anastomosis; for the ureter or urethra is usually cut transversely or else obliquely, and in either situation the lumen of the small tube is directly involved in the anastomosis, and so becomes constricted if the site of anastomosis contracts.

One popular method of averting this complication has been the use of the "fish mouth" incision, which entails slitting both sides of the ureter or urethra so that there are two flaps which offer a large periphery for anastomosis. But this method still presents a small cross section of the urethra or ureter, and constriction can occur even though it is less likely with this technic than with some of the others that have been described. One major objection to this method is that the fish mouth flaps have a rectangular shape which gives rise

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FIG. 1

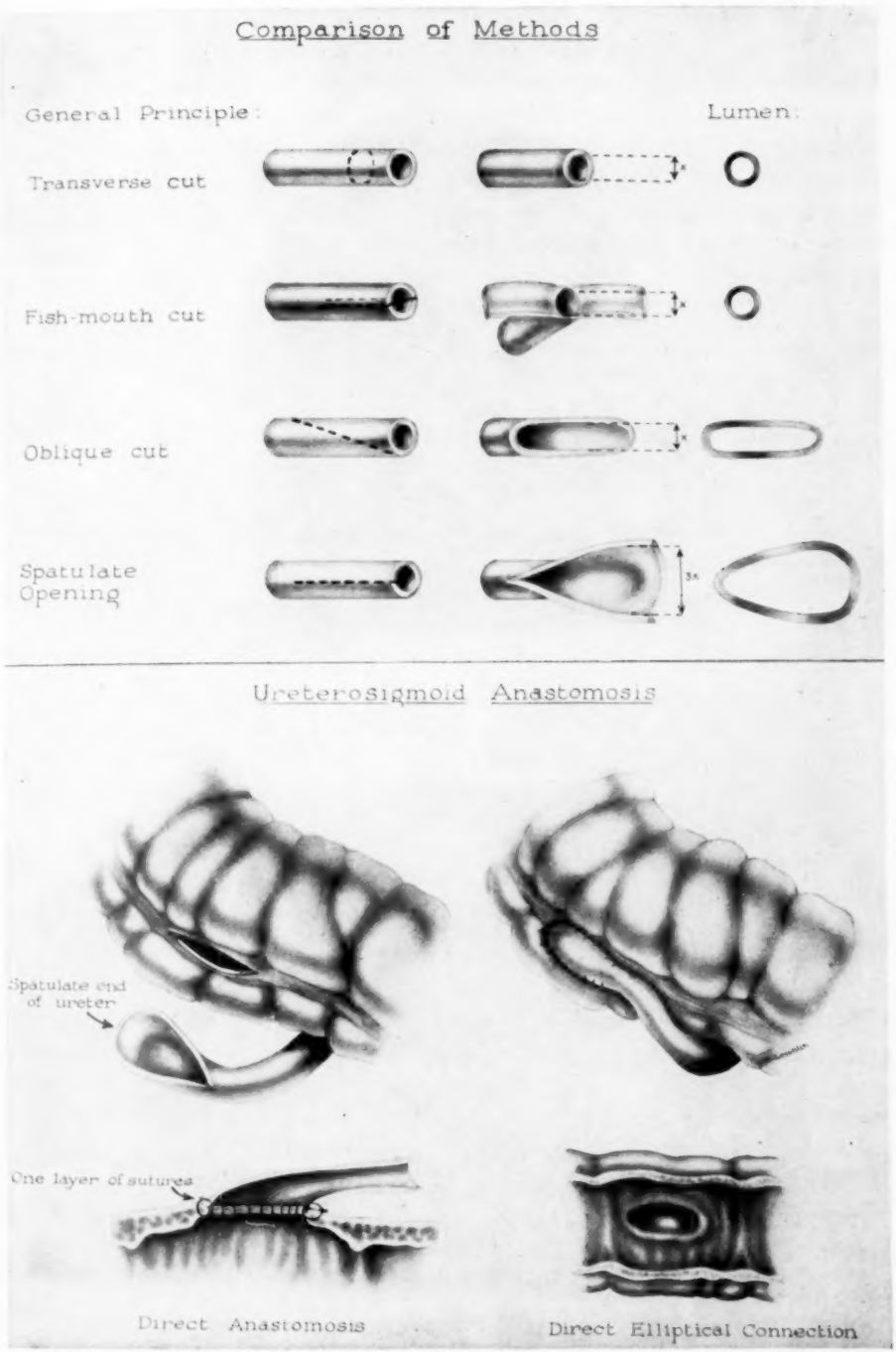


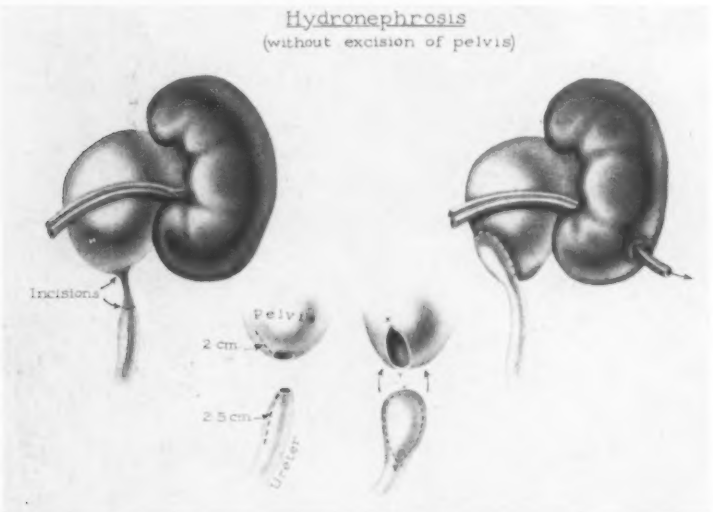
FIG. 2

FIG. 1.—Comparative diameters of terminal ureter prepared by various technics.
FIG. 2.—Anastomosis of ureter to colon by direct elliptical anastomosis provides maximum diameter of stoma.

to difficulty in obtaining close opposition with skin or mucous membrane in making an anastomosis.

The principle of elliptical connection which is made possible by a single slit at the terminal end of the ureter or urethra appears to overcome the tendency to constriction in the lumen. When the tube is slit in this manner, its terminal portion becomes spatulate in shape with a diameter pi times the diameter of the original tube. Furthermore, when the spatulate end is utilized in making a direct anastomosis to the skin or to another viscus, the actual caliber of the smaller tube is in no way jeopardized by healing of the anastomosis, since only one stitch directly involves its circumference. When this technic is employed,

FIG. 3



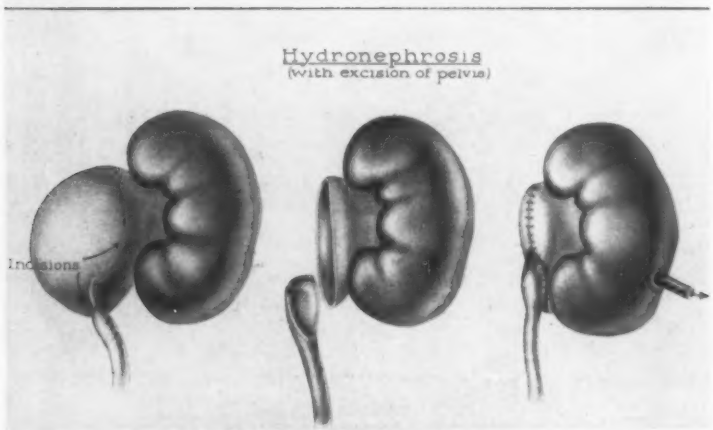


FIG. 4

FIG. 3.—Principle of elliptical anastomosis applied to correction of congenital hyronephrosis.

FIG. 4.—When pelvis is large the redundant portion is excised and elliptical connection with upper ureter carried out.

any tendency to constriction at the point of epithelial union will involve only the large circumference of the stoma and will not, in so doing, cause a decrease in caliber of the tubes that are connected by the anastomosis.

We first applied this principle of anastomosis in performing ureterosigmoidal transplantation (Fig. 2), hoping to eliminate some of the disadvantages inherent in previous transplant operations. Most of the earlier technics employed the tunnel principle in the belief that such an arrangement provided a valve to protect the upper urinary tract from reflux. Whether a valve mechanism actually operates effectively in this circumstance has never been deter-

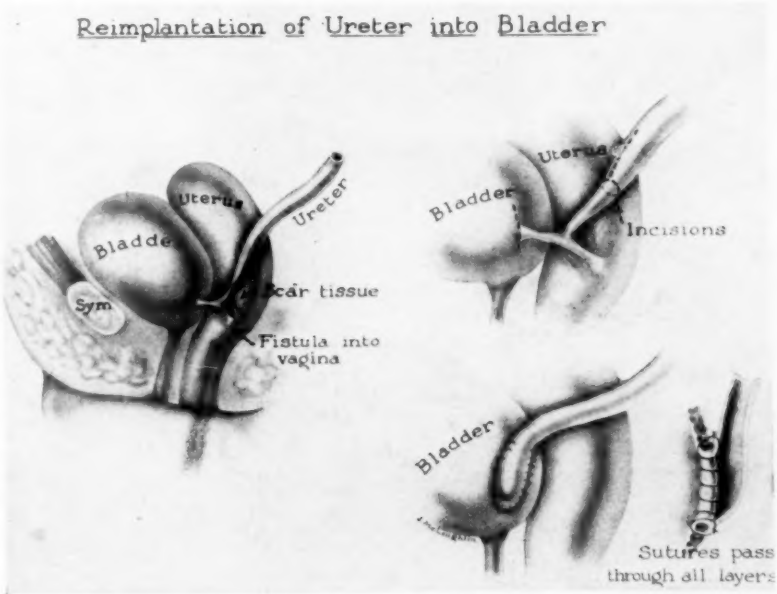


FIG. 5.—Reimplantation of ureter into bladder by elliptical anastomosis.

mined. Many investigators have held the view that reflux is prevented by unimpeded peristalsis in a normally functioning ureter; and that the natural oblique insertion of the ureter into the bladder is a fortuitous arrangement rather than a protective one.

The tunneling operations of uretero-intestinal anastomosis are often complicated by postoperative hydronephrosis due to stricture at the site of anastomosis, and there are three frequent sites of obstruction: concentric constriction of the terminal ureter that projects into the lumen of the bowel; fibrosis in the tunneled area; and peritoneal constriction at the point where the ureter enters the site of anastomosis.

Ureterosigmoidal anastomosis by direct elliptical connection avoids all of these points of constriction, and has demonstrated its value in the uniform avoidance of ureteral and renal dilatation in laboratory animals and in over 20 patients that have been operated upon during the past year at the University

FIG. 6

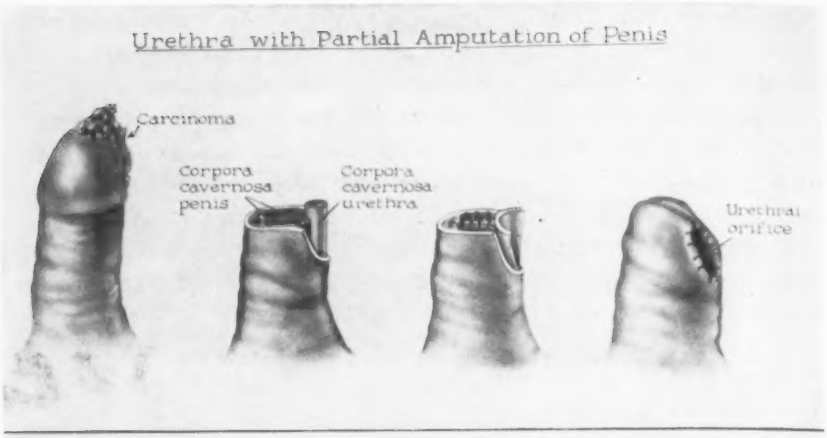


FIG 7

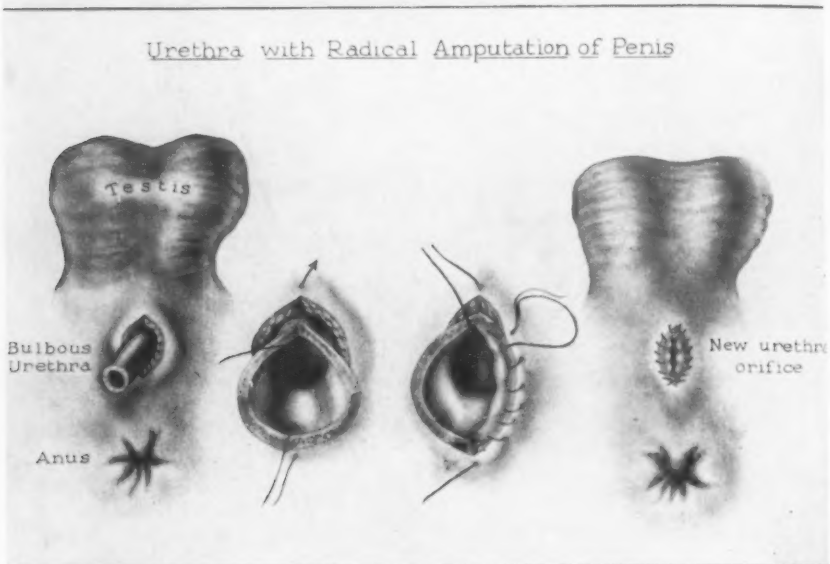
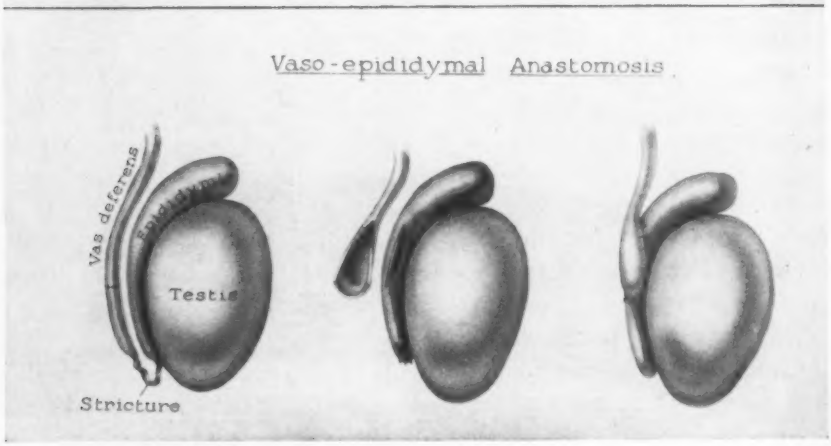


FIG. 8



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of Michigan Hospital. Another advantage of this technic has been demonstrated in the successful transplantation of grossly dilated ureters in four of our patients: two of the latter had far advanced bilateral hydro-ureters and hydronephrosis. Personal communications from many surgeons who have performed this operation since the preliminary report of the procedure in May, 1948, have revealed that it has been successful in nearly a hundred cases at the present time.

The principle of elliptical connection has also been applied successfully in reimplanting the upper end of the ureter for the treatment of congenital hydronephrosis. When there is a relatively small renal pelvis (Fig. 3) the ureter is severed and a terminal slit is made on one side for a distance of about 1 cm., then a vertical incision of equal length is made at a dependent point in the renal pelvis and direct anastomosis is made. When a large and redundant pelvis is encountered (Fig. 4) it is excised and anastomosis of the spatulate upper ureter is made at the lower end of the incision in the pelvis. We have not employed a splint at the site of anastomosis, but have directed the urine by nephrostomy for two weeks.

This same technic of anastomosis has been employed successfully in three cases for the reimplantation of the lower ureter into the bladder. In the case illustrated by the artist's sketches (Fig. 5) there was a ureterovaginal fistula, and the ureter and renal pelvis were moderately dilated. The operative approach was made above the site of previous operation, and the ureter was picked up retroperitoneally and followed downward to the area of cicatrix, where it was cut across and a slit was made at a favorable site on its inferior aspect and direct anastomosis was made between the two viscera by interrupted catgut sutures, the stitches passing through all coats of both structures. Diversion of the urine was effected for two weeks by means of a T-tube placed in the ureter above the site of anastomosis. Six weeks after operation excretory pyelograms showed that the ureter and kidney had returned to normal size. A cystogram was made after the bladder had been filled with sodium iodide solution to a point of painful distention, yet there was no reflux of the contrast medium that could be seen on the roentgenograms that were made under these conditions.

Elliptical anastomosis has been employed advantageously in connection with the performance of cutaneous ureterostomy in two cases, and these comprise the sole instances in our experience where stricture at the mucocutaneous junction has been avoided.

Four patients with cancer of the penis have had amputations in which elliptical anastomosis of the urethra to the skin has been employed. In two cases a local amputation was performed (Fig. 6) and the method was found to

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FIG. 6.—Following partial amputation of penis, this method provides a satisfactory meatus.

FIG. 7.—Perineal urethrostomy by elliptical anastomosis prevents stricture.

FIG. 8.—Anastomosis of vas deferens to epididymis is simplified by using elliptical connection.

simplify the technic of operation. Follow-up examination of both patients demonstrated the new meatus to be free from stricture.

The bugbear of stricture in perineal urethrostomy following radical amputation of the penis is notorious, and has been a serious complication of the operation. In two patients who had radical amputation the bulbous urethra was anastomosed to the perineal skin (Fig. 7) by direct elliptical connection, and strictures have been avoided in both instances.

Another situation in which the principle was successfully employed involved the anastomosis (Fig. 8) of the vas deferens to the epididymis in treating sterility due to a congenital stenosis in the duct of the epididymis. The patient had been shown by testicular biopsy to have normal spermatogenesis, yet his semen contained no spermatozoa. A slit 1 cm. long was made in the globus major of the epididymis and fluid obtained from it was found to be made up of active sperms. Elliptical anastomosis between the slit terminal vas deferens and the incised epididymis was easily effected, and six months after operation the patient had a semen which contained spermatozoa in normal number and having normal activity.

The principle of elliptical anastomosis is manifestly not a new concept, because the technic has previously been utilized in all fields of surgery. But the distinct advantages of the method in the field of urologic surgery apparently have never before been asserted. The clinical value of elliptical anastomosis is demonstrated by the various operations that have been described in the present communication.

Discussion.—Dr. Robert Lee Payne, Norfolk, Va.: I am intensely interested in Doctor Nesbit's paper for several reasons. It will be patent in my discussion. Whenever a ureter is divided, stricture inevitably and always results unless there is a mucosal anastomosis made immediately after the division of the ureter. That is why Simon in 1869 first recommended a nephrectomy for ureteral fistula and this was followed by attempts of anastomosing the ureter in the bowel, the skin, the bladder and the vagina. The principal objection to all methods of anastomosis has been a development of stenosis; and, second, the possible danger of ascending infection from regurgitation. With the flush anastomosis to the bladder wall, stricture is most liable to result.

In 1908, in a monograph on this subject, I stated in my article that I did not believe regurgitation took place, or at least did not account for ascending infection. In none of my cases have I ever seen infection, present at the time of operation, fail to clear up after the split double flap type of anastomosis; and I stated I did not believe there is a normal ureteral valve at the ureteral orifice to prevent regurgitation. Pozzie, Modkinsky and Desnos report leakage of urine from the bladder through the vesical stump of a divided ureter and Hartman reports leakage from the vesical stump following a nephrectomy.

Since in all of my cases of ureteral fistulae infection has cleared up rapidly following the double flap method of anastomosis, I am led to believe that regurgitation plays a small role, if any, in ascending infection following ureterovesical implantation. My idea is that the bladder wall contracts around the double flap type of anastomosis and possibly prevents regurgitation. The musculature of the bladder is composed of an inner and outer longitudinal layer and a middle circular layer. If the flap anastomosis is made at the summit of the bladder and the ureter thus passed through the entire bladder wall, hence through this mesh-like arrangement of muscle fibers, it seems reasonable to believe that

vesical contraction would produce a valve-like constriction of the ureter and thus prevent any forcible regurgitation.

In 1903 Van Hook recommended splitting the ureter on one side, as Doctor Nesbit advises, thus making an elliptical flare; and in these cases the ureter was anastomosed flush to the bladder and this resulted in stricture. By my method of anastomosis the ureter is split on both sides and these lateral flaps are then drawn into the bladder by traction sutures and fixed. Regarding the fixation of the flaps, I recommended that a layer of mucous membranes on either side of the vesical incision be removed, thus securing for the flaps an approximation of connective tissue to connective tissue. Two cases of this flap-type of anastomosis were reported by me, with illustrations, in the Journal of the American Medical Association, October 17, 1908, Page 1321. One of these cases had the left kidney lowered to accommodate for a shortened ureter.

Bovee successfully lowered the kidney for a shortened ureter in dogs; but my case reported 1908 was the first time this was done and reported in the human.

Over a period of nearly 43 years, I have never had the opportunity to do this operation but 12 times. In one of my patients the surgeon had operated and tied both ureters, and the individual had been totally anuric for exactly six days before the diagnosis was made. I remember Doctor Starr Judd telling me that he had seen an individual with both ureters ligated, who had been totally anuric for nine days. In my patient just referred to, who had been totally anuric for six days, one of the ureters functioned normally through the bladder after the ligature had been removed; but the other ureter developed a ureteral fistula after removing the ligature and this ureter 12 weeks later was implanted into the bladder by the split double flap method shown to you in the slides on the screen.

This flap method of anastomosis has been successfully used by me, not only in uniting the ureter to the bladder, in resections of strictured areas at the uretero-pelvic junction in the kidney, but also in planting the ureters into the bowel.

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ANNALS OF SURGERY

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THE PATHOGENESIS OF HYPERTHYROIDISM*

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INTRODUCTION

HYPERTHYROIDISM results from the release of an excess of the hormone normally produced by the acinar cells of the thyroid gland. Such an excess of secretion may be produced by a localized group of cells within the thyroid gland, a so-called adenoma, or it may be due to a generalized overaction of the cells of the thyroid gland. The latter results from increased production of the thyrotropic hormone. Evidence will be advanced to show that the increased production of this thyrotropic hormone which is secreted by the glandular hypophysis results in turn from an increased secretion of the neural hypophysis, the latter being under nervous control from the supraoptic and the paraventricular hypothalamic nuclei. The hypothalamus, including these two nuclei and the centers of the sympathetic and the parasympathetic systems as well, is subject to excitation and suppression from the central nervous system; and as a consequence of the exteroceptive and interoceptive impulses which reach the latter, the neural hypophysis may be influenced. It must be inferred that different subjects differ constitutionally with respect to the degree to which this chain of events activates the hypophysis; the action as such may be considered a normal one for the regulation of visceral functions. Evidence to support these statements will be presented from experimental and clinical data.

EXPERIMENTAL DATA

Source of thyrotropic hormone. In previous reports (Heinbecker,[1,12] 1944, 1946) it was shown that following denervation of the neural hypophysis in the dog (Fig. 1), either by section above the median eminence (puncture, Type 1) or by a transverse section caudal to the stalk in front of the mammillary bodies (puncture, Type 2) there occurs a change in the cytology of the glandular hypophysis which is characterized by a marked loss of basophile cells and an increase in eosinophiles (Fig. 2). If animals so operated on are compared with animals simply or totally (median eminence included) hypophysectomized, it is found that in both atrophy of the thyroid gland occurs (Fig. 3). This indicates that the atrophy of the thyroid gland is brought about by loss of the basophile cells, because the puncture type dog has an adequate number of active eosinophiles left. Their activity is evidenced by a decrease in circulating lymphocytes and by a decrease in insulin sensitivity. In females there occurs also a loss of ovarian follicles, and in males a failure of maturation of

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† Recipient of a grant-in-aid of research from the Commonwealth Fund and the United States Public Health Service.

the spermatocytes. In these puncture dogs the adrenal glands and the interstitial tissues of the ovary and of the testis remained normal. On the basis of such evidence it is concluded that the basophile cells of the glandular hypophysis are the source of hormones trophic to the thyroid gland, to the ovarian follicles, and to the tubule cells of the testis. From these experiments it may be concluded also that decreased activity of the supraoptic and the paraventricular

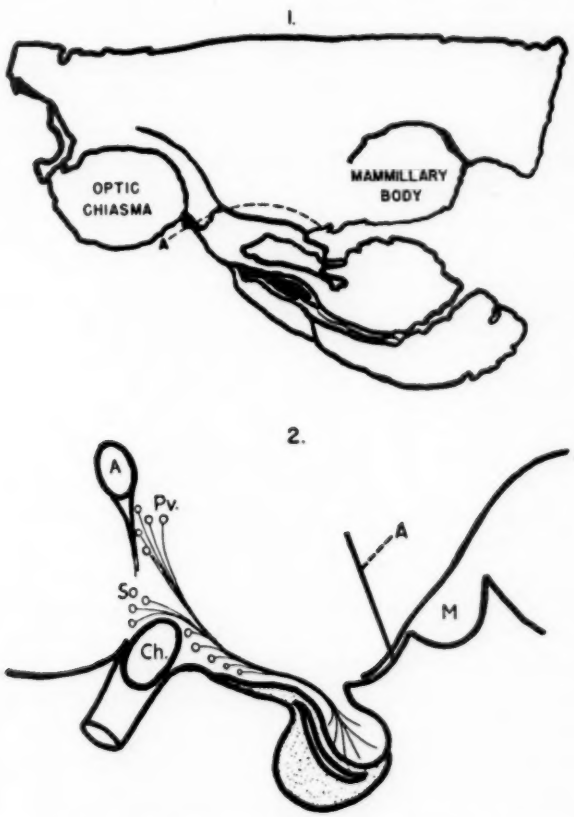


FIG. 1.—Diagram to indicate operations to denervate the neural hypophysis.

1. Complete denervation called Puncture Type 1, performed through the oral approach.

2. Partial denervation, Puncture Type 2, by severance of afferent fibers from the caudal and superior areas to the paraventricular and supraoptic nuclei, performed through the temporal approach.

of the hypothalamus is responsible for the loss of hypophysial basophile cells noted following puncture operations. The decreased activity of these nuclei reduces the formation of posterior lobe hormone, and thus is responsible for the loss of basophile cells in the glandular hypophysis. Other influences which modify basophile cell maturation will be considered later in this presentation.

EFFECT OF EXOGENOUS POSTERIOR PITUITARY HORMONE ADMINISTRATION ON THE CYTOLOGY OF THE GLANDULAR HYPOPHYSIS

Exogenous whole posterior lobe hormone was administered to two female and one male dog for periods varying from 28 to 45 days. During the period of hormone administration the dogs were kept in metabolism cages and fed a mixture of dog biscuits and horse meat. Daily urine collections were made. Periodically blood cholesterol and blood sugar determinations were run. On two of the dogs frequent total and differential blood counts were made before and during the period of hormone administration.

The dogs remained in good general health, their urine output was slightly but not significantly decreased, their appetite remained good. In two of the dogs given 15 and 90 units respectively of posterior lobe hormone for a period of 60 days, the blood circulating lymphocytes gradually increased to 30 per cent above the control values obtained before the period of hormone administration began. There was first an increase in blood cholesterol of 15 per cent, with a later decrease to a little below the preinjection level.

TABLE I.—*Cell Counts of Two Dogs Given 45 Units Posterior Pituitary Hormone; Dog 1 for 28 Days and Dog 2 for 45 Days.*

	Eos.	Baso.	Chromo.
Dog 1	58.6%	14.6%	26.8%
Dog 2	51.9%	17.2%	30.9%
Average normal controls	38.5%	9.2%	52.3%

At the end of the period of observation the dogs were sacrificed and complete autopsies performed. The pituitary glands were fixed in 10 per cent formalin, serially sectioned at 5 microns, and differentially stained according to the method of A. T. Rasmussen. The thyroid gland, the gonads, and other endocrine organs were studied in detail. The percentage of basophile cells was increased in the glandular hypophysis as a result of posterior lobe hormone administration (Table I). The thyroid gland showed actively secreting cells (Fig. 3). The ovaries showed an increase in the thickness of the germinal layer due to many large growing follicles. The testes showed active spermatogenesis.

Since the major result of excess posterior lobe hormone on the glandular hypophysis of the normal animal is an increase of basophiles and a decrease in their number follows a decrease in the amount of posterior lobe hormone, it is concluded that the basophiles are normally regulated in number and in the amount of their secretion by the activity of the neural hypophysis.

EFFECT OF THYROIDECTOMY, CASTRATION AND HYPERTHYROIDISM ON THE GLANDULAR HYPOPHYSIS

It has been shown in this laboratory and by others (Severinghaus, 1935,[2] and Zeckwer *et al.*, 1935[3]) that removal of the thyroid gland or of the gonads

or of both together results in a marked increase in the hypophysial basophile cells. Such basophiles may become degranulated and filled with clear material. The interpretation made is that removal of the thyroid, or the gonads, or of both together, permits an increase of hypophysial basophile cells, which in time become altered cytologically because of an accumulation of secretory products. These are not released or, if released, are ineffective, because of a lack of thyroid, of follicular, or of seminiferous tubule hormone. The same condition results eventually after denervation of the neural hypophysis. Up to two years after such an operation the effect is a loss of hypophysial basophiles, with resultant depression of thyroid and gonad function leading to eventual atrophy of the thyroid, of the ovarian follicles, and failure of maturation of the spermatocytes. Eventually, such atropic changes will be reflected in the cytology of the glandular hypophysis by an increase in basophile cells (unpublished data in this laboratory). The hormones of the altered basophile cells are unable to restore to a normal state the atrophic glands to which they are trophic normally.

TABLE II.—*Effect of Desiccated Pork Thyroid 0.1 Gm. per Kg. Per Day for 42 Days on the Cytology of Glandular Hypophysis of the Dog.*

	Eos.	Baso.	Chromo.
Dog X43	44.1%	6.6%	49.3%
Dog X36	40.3%	3.3%	56.4%
Average normal controls	38.5%	9.2%	52.3%

In other experiments it was found that the administration to two dogs of thyroid gland substance (0.1 Gm. per Kg. body weight per day for 42 days) did not increase, but rather tended to decrease the basophile cells of the hypophysis (Table II). The eosinophile cells showed a slight increase. Severinghaus, Smelson and Clarke[2] (1934) on the other hand, found in thyroid-fed rats an increase in basophiles cytologically indistinguishable from that found following castration or thyroidectomy. The hyperthyroid rats showed a pronounced increased acidophilia. The acidophile changes were in direct contrast to those seen after thyroidectomy in the rat in which the acidophiles revert entirely to chromophobes, or after castration, where they decrease in size and number. Apparently the response of the glandular hypophysis to exogenous thyroid substance varies with the animal species, with the amount, and with the duration of thyroid administered (Romeis,[4] 1940).

Our experience with the cytology of the glandular hypophysis of man, with hyperthyroidism, has been limited due to lack of available material. In a typical case of a man of 51 years who died without therapy in thyroid crisis after 20 years of hyperthyroidism due to diffuse overaction of the thyroid acinar tissue (BMR +67 per cent) there is shown a marked increase in basophile cells, and a decrease in eosinophile cells (Fig. 4).

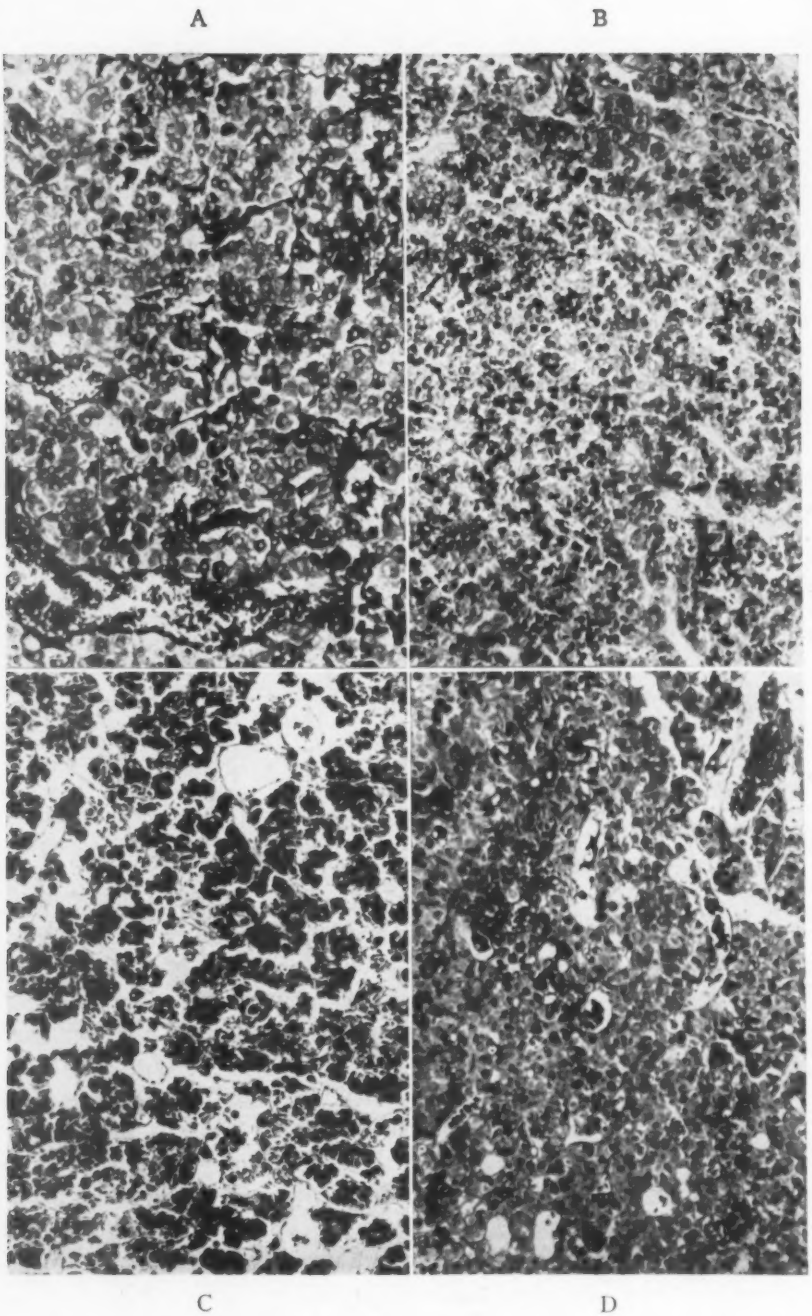


FIG. 2.—A. Photomicrograph x95 of glandular hypophysis of normal dog showing eosinophiles 39.8 per cent, basophiles 9.4 per cent, chromophobes 50.8 per cent.

B. Photomicrograph x95 of glandular hypophysis of puncture dog Type 1 showing eosinophiles 64.2 per cent, basophiles 0.0 per cent, chromophobes 35.8 per cent two years following puncture operation.

C. Photomicrograph x95 of glandular hypophysis of puncture dog Type 2, one year after operation showing eosinophiles 52.5 per cent, basophiles 1.5 per cent, chromophobes 46 per cent.

D. Photomicrograph x95 of glandular hypophysis of normal dog given 25 units posterior lobe hormone for 28 days showing eosinophiles 51.9 per cent, basophiles 17.2 per cent, chromophobes 30.9 per cent.

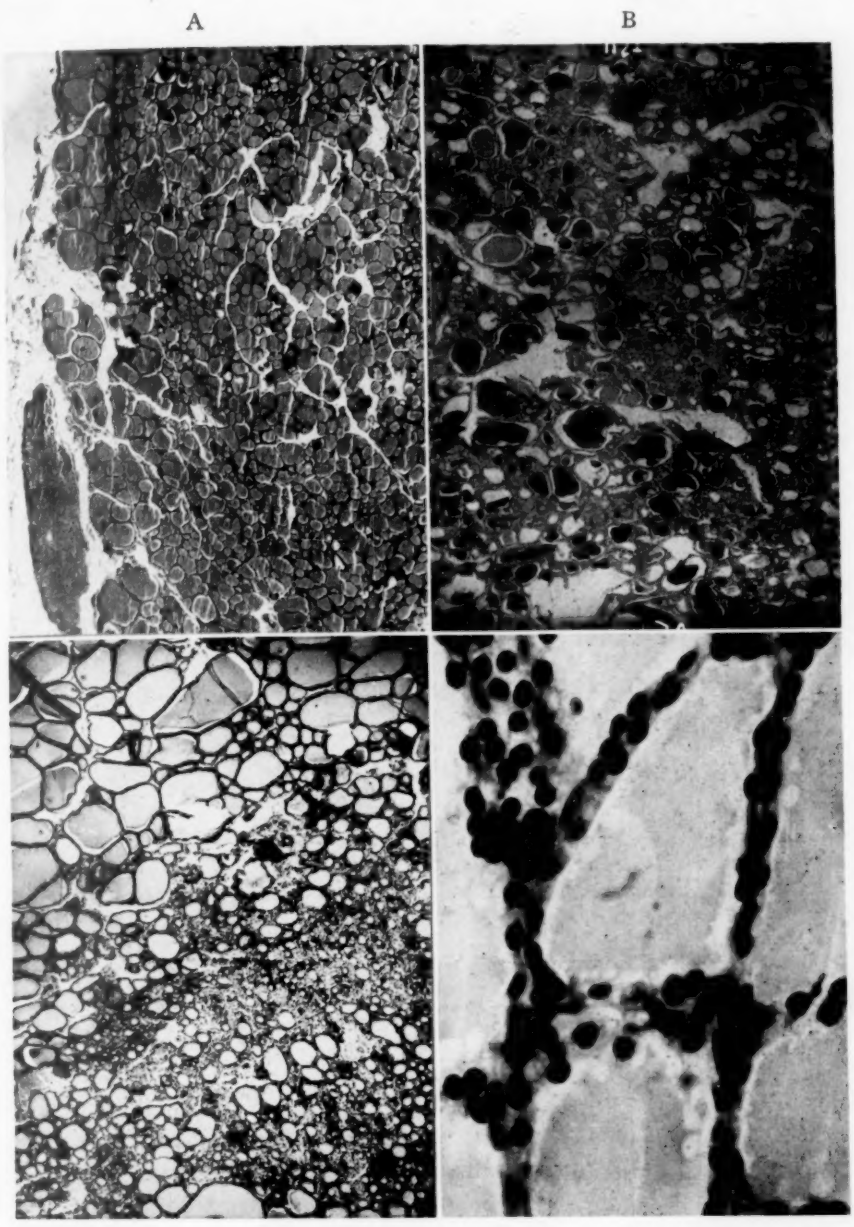
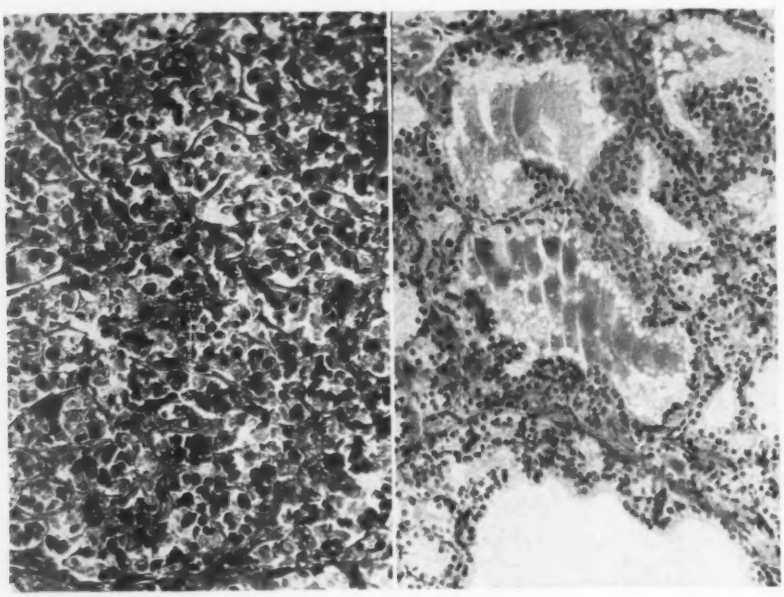


FIG. 3.—A. Photomicrograph of thyroid gland of normal dog.
B. Photomicrograph of thyroid gland of totally hypophysectomized dog.
C. Photomicrograph of thyroid gland of puncture dog Type 1.
D. Photomicrograph x475 of the thyroid gland of normal dog after 28 days of posterior lobe extract. Note atrophic state of thyroid gland of B. and C. on comparison with A. Note active acinar tissue in D.

EFFECT OF HYPOTHALAMIC PUNCTURE AND OF TOTAL HYPOPHYSECTOMY ON THE PARATHYROID GLANDS

Material and data were obtained on four Type 1 puncture dogs and four totally hypophysectomized dogs. They were sacrificed two or more years following their operation. Autopsy studies revealed that in the Type 1 puncture dogs, and in totally hypophysectomized dogs, the parathyroid glands became enlarged to four to six times their average normal size for dogs of similar size and age. Marked parathyroid enlargement also was found in two totally hypophysectomized and thyroidectomized dogs sacrificed two years after the



A B

FIG. 4.—A. Photomicrograph x90 of human glandular hypophysis from patient with marked hyperthyroidism showing basophile cell preponderance. B.-Photomicrograph x90 of thyroid gland of patient C., Figure 7, showing actively secreting acinar tissue.

removal of the hypophysis and the thyroid glands. On the basis of this evidence, it is concluded that the basophile cells are inhibitory to the parathyroid glands. The microscopic examination of such enlarged parathyroid glands (Fig. 5) reveals that the enlargement is due to an increase in normal appearing closely packed cells. Because of this it is concluded that they are functionally active. Still, in the dogs with such enlarged parathyroid glands the serum calcium and serum phosphorus values remained within normal limits and no demineralization of the bones occurred.

One Type 1 puncture dog with enlarged parathyroid glands (Fig. 5) was sacrificed seven and one-half years after the original operation. Hypophysial basophile cells essentially absent up to two years after such an operation had

returned, and their number was greatly increased, being 40 per cent of the differential count as compared with a normal of nine to ten per cent. It is significant to note that the basophile cells are degranulated and filled with clear material considered by us to represent a retained secretory product. Because

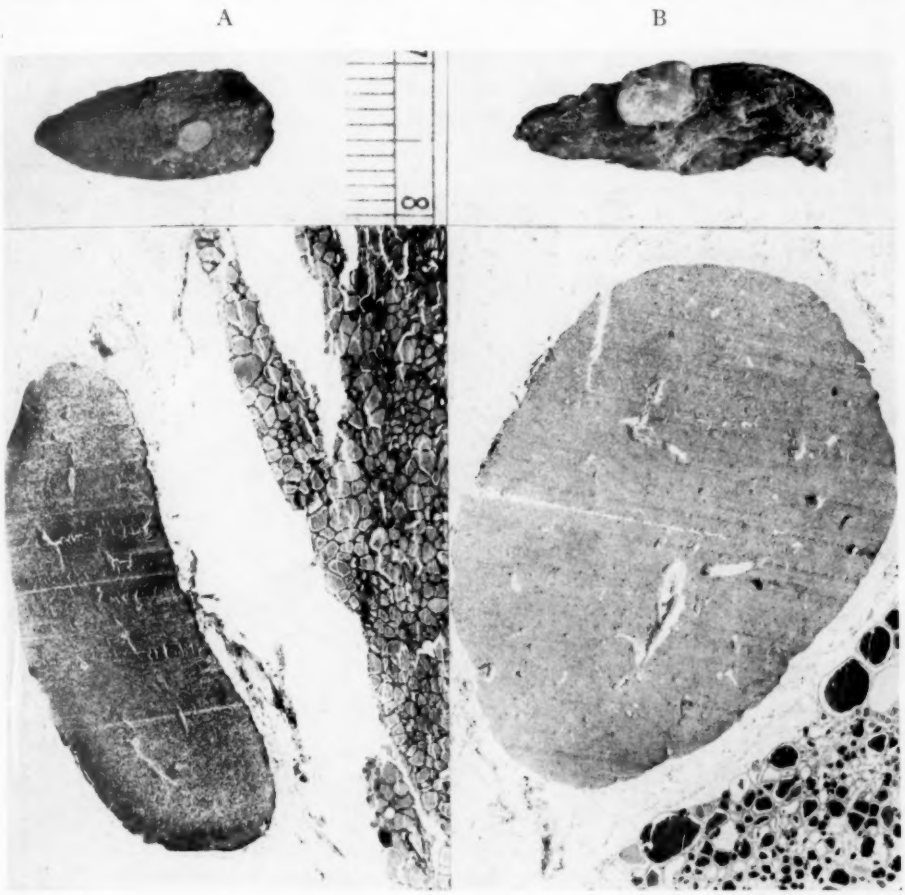


FIG. 5.—A. Photograph of parathyroid gland of normal dog.
B. Photograph, same magnification as in A. of thyroid gland of puncture dog Type I, seven and one-half years after operation, showing marked increase in size of parathyroid gland.
C. Photomicrograph x12 of largest normal parathyroid gland encountered.
D. Photomicrograph x12 of parathyroid gland of totally hypophysectomized dog two years after operation. Note the gland is composed entirely of parathyroid cells.

of the persistent atrophic state of the thyroid gland and the ovaries, however, it is inferred that the secretion had not been released or was not effective.

EXOPHTHALMOS

Experimental data. Loeb and Friedman[5] (1931) and Marine and Rosen[6] (1933) produced exophthalmos by the administration of whole pituitary and

of thyrotropic hormone in thyroidectomized guinea pigs. Dobyns[7] (1946) produced exophthalmos in the guinea pig by the administration of thyrotropic hormone to both normal and thyroidectomized animals. His studies of the orbital tissues showed edema and early fatty infiltration into the muscles. From such studies it is evident that thyrotropic hormone alone can cause exophthalmos in some animals. The effect disappears with the cessation of

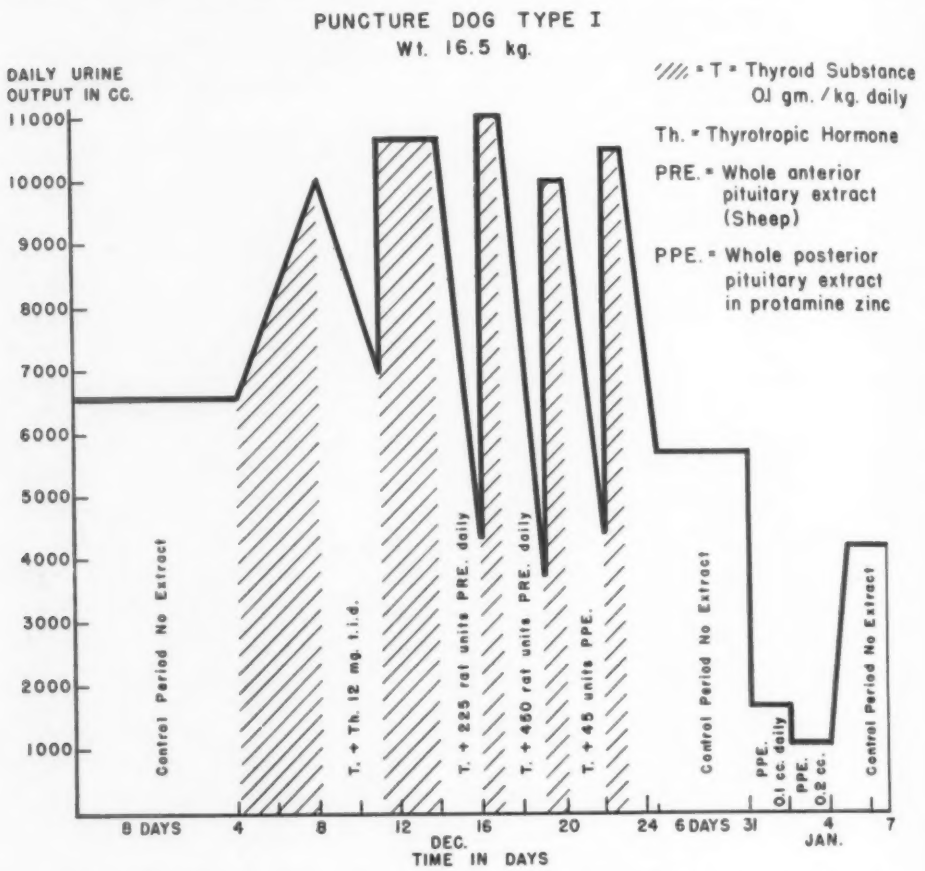


FIG. 6.—Chart to show diuretic effect of thyroid substance in a diabetes insipidus dog due to Puncture Type I. It shows also the antidiuretic effect of purified thyrotropic hormone, of whole anterior pituitary extract, and of whole posterior pituitary extract in protamine zinc.

hormone administration. Significantly the injection of pituitary extracts in animals produces both in the eye muscles and in skeletal muscles changes that closely resemble those found in corresponding muscles in man suffering from Graves' disease. The orbital tissues appear to be more susceptible to the water retaining influences of the hormones, although skeletal muscles may be similarly but less severely affected.

In this laboratory, studies pertinent to the problem of exophthalmos were made on three dogs. Two were totally hypophysectomized, and in one the

neural hypophysis was denervated. As a result of the operations all three dogs exhibited marked diabetes insipidus. The two totally hypophysectomized dogs were given daily administration of thyroid gland powder, 0.1 Gm. per Kg. throughout the experimental period. In addition, they were given at stated intervals doca, whole adrenal cortical extract, anterior pituitary extract (preloban), purified thyrotropic hormone, and posterior lobe hormone. The dosages used in the dog with the neural hypophysis denervated, and the results obtained, are shown in Figure 6.

From the results of the experiments it can be stated that preloban, thyrotropic hormone, and posterior lobe hormone are markedly antidiuretic. They, therefore, would tend to retain water in the tissues. This finding is offered as the mechanism through which they produce exophthalmos in animals and in man.

Thyroid extract has been shown to be markedly diuretic in the hypophysectomized and the puncture type dog. It would, therefore, tend to compensate for the water retaining influence of the thyrotropic hormone itself. Of similar import is the observation that removal of the thyroid gland in dogs stops the temporary diabetes insipidus which follows simple hypophysectomy (Mahoney and Sheehan,[8] 1935). This observation was confirmed in this laboratory. It follows that exophthalmos might well become augmented by a reduction in circulating thyroid hormone below its normal level.

In two other dogs chronic adrenal deficiency was produced by bilateral adrenalectomy. The dogs were maintained in good condition by the implantation of pellets of desoxycorticosterone, one for a period of nine months, the other for 14 months. At autopsy a generalized increase in lymphoid tissue was noted. Complete and differential white blood counts made periodically revealed a gradual increase in the number of circulating lymphocytes. Thus in one dog four months after operation the blood picture was as follows:

RBC	WBC	EOS	BASO	STABS	SEGS	LYM	MONO
5.17	15,875	13.5%	0 %	0.5%	43 %	42 %	1 %

One year after operation the counts were:

6.96	14,600	5.0%	0.5%	.8%	24.3%	67.8%	1.7%

Average normal control counts for dogs in this laboratory were:

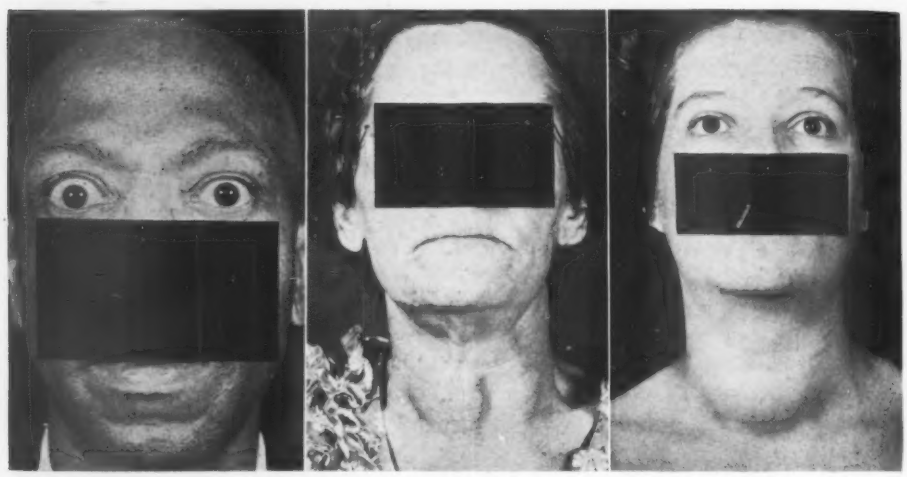
7.1	12,500 ±5000	5.2%	0 %	1.1%	62.1%	28.6%	3.0%

In other experiments it was shown that in the dog the administration of thyroid powder 0.1 Gm. per Kg. tends to lower rather than raise the number of circulating lymphocytes. A similar effect was obtained by the administration of purified thyrotropic hormone. For these reasons the increase in circulating lymphocytes which characterizes Graves' disease are taken to indicate hypofunction of the eosinophile-adrenal hormone complex rather than hyperfunction

of the basophile-thyroid hormone complex, because the latter would decrease rather than increase the circulating lymphocytes.

Illustrative Case: A 45-year-old colored male was admitted to Barnes Hospital January 10, 1947, because of a bulging of the right eye and diplopia. Investigation revealed an indefinite enlargement of his thyroid gland; BMR +26. His blood cholesterol was 185 mg. per 100 cc.; and WBC was 9000, with circulating lymphocytes 34 per cent. After study he was discharged for clinic treatment with propyl thiouracil 50 mg., t.i.d. He was readmitted to the hospital September 15, 1947, with bilateral malignant exophthalmos and keratitis (Fig. 7). His BMR now was —26; his blood cholesterol 277 mg. per 100 cc. A bilateral maxillary sinusotomy and ethmoidectomy was performed to save his sight.

The case illustrates two well known facts: (1) that exophthalmos frequently is associated with hyperthyroidism and (2) that exophthalmos frequently becomes more marked with the lowering of basal metabolism by treatment.



A B C

FIG. 7.—A. Photograph of patient showing malignant exophthalmos. B. Photograph of patient with local adenomatous nodule. C. Photograph of patient exhibiting Graves' disease.

Clinical and pathologic studies have established with reasonable certainty that the bulging of the orbital contents is associated with swelling of the orbital muscles, connective tissue, and fat, together with a marked increase in lymphoid tissue (Naffziger and Jones,[9] 1932). After prolonged edema of the muscles, replacement of muscle cells with fibrous tissue cells is a natural consequence. An hypothesis is offered that the edematous swelling of the orbital tissues is due to the water retaining effects of thyrotropic hormone in particular, and possibly of posterior lobe hormone as well. The lymphoid tissue increase is considered due to depression of the adrenal cortex which accompanies marked hyperthyroidism. Hyperthyroidism not infrequently occurs in patients with Addison's disease (Brenner,[10] 1928) and (Crooke and Russel,[11] 1935).

THYROID-PARATHYROID INTERRELATIONSHIPS

Experimental data. To investigate thyroid-parathyroid interrelationships dogs were used as experimental animals. They were kept in metabolism cages and fed dog chow and horse meat. The following operations were carried out on the hypophysis through the oral approach: (1) removal of the glandular and neural lobes (simple hypophysectomy); (2) removal of the adenohypophysis and the entire neural hypophysis (total hypophysectomy); (3) denervation of the neural hypophysis by section above the median eminence without removal of the adeno or neural hypophysis (puncture, Type I); (4) simple hypophysectomy plus total thyroidectomy.

Two dogs were kept in cages as normal controls. Three dogs were simply hypophysectomized, two were totally hyposectomized, two were punctured (Type I) and two were simply hypophysectomized and thyroidectomized.

The dogs were kept for periods of one to seven years before being sacrificed and completely autopsied. During this time none of the dogs showed variations in their serum calcium or serum phosphorus beyond the limits of normal. Analysis of the findings permit the following statements to be made:

1. Caging of normal dogs on the diet used did not lead to parathyroid gland enlargement.

2. Two years or more after simple hypophysectomy, after total hypophysectomy, after puncture, Type I, and after simple hypophysectomy plus thyroidectomy, definite enlargement of parathyroid glands occurred.

3. The loss of hypophysial basophile cells, or their degranulation, is

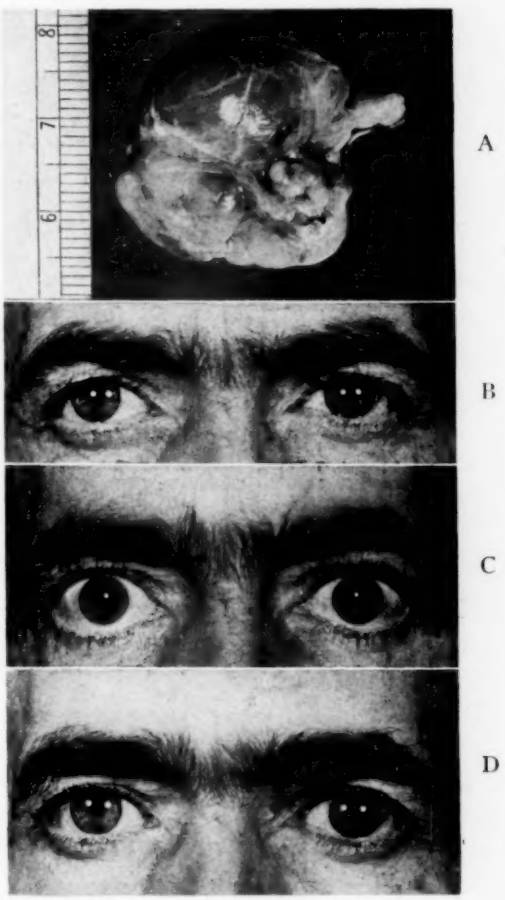


FIG. 8.—A. Photograph of parathyroid adenoma removed at operation from patient shown in B, C and D.

B. Photograph of patient's eyes 18 days after operation. Note eyes are normal. Preoperative BMR —16.

C. Photograph of patient's eyes 28 days after operation. Note marked exophthalmos. BMR +26.

D. Photograph of patient's eyes six months after operation. Note return of eyes to normal. BMR normal. Iodine administered for 10 days. No operation on thyroid gland.

associated with atrophic changes in the thyroid gland and with parathyroid enlargement.

On this evidence it is concluded that the hypophysial basophile cells exert an inhibitory influence on the parathyroid glands. Their loss or degranulation permits parathyroid gland enlargement.

Illustrative Case: A white male, 36 years of age, was admitted to Barnes Hospital because of nausea, vomiting and weight loss of three years' duration. Nine months before admission lumps appeared on his lower right jaw and on his left tibia. His serum

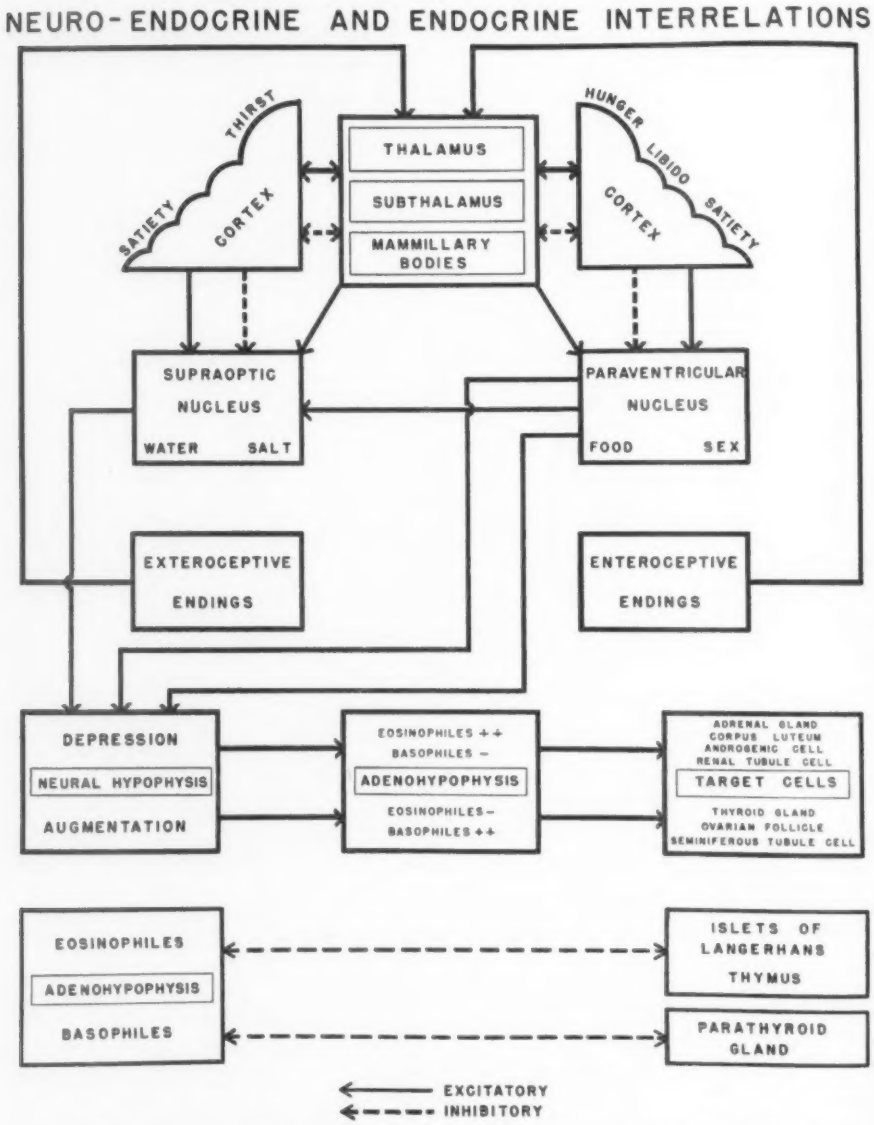


FIG. 9.—Diagram to show manner in which influences from the central nervous system, acting through the hypothalamus on the neural hypophysis, can effect changes in other endocrine glands.

calcium was found to be 17.2 mg. per 100 cc.; his serum phosphorus 5.4 mg. per 100 cc.; alkaline phosphatase 26 Bodansky units; BMR —16 per cent; urine concentration to 1013; and urea clearance 59 per cent average normal. A biopsy of the tibia showed fibro cystic disease of the bone. A diagnosis of a parathyroid tumor was made. On March 30, 1948, an adenoma of the parathyroid was removed (Fig. 8). Following his operation the patient developed hyperthyroidism with exophthalmos (Fig. 8). On May 7, 1948, his BMR was +28. No enlargement of the thyroid gland was evident. The patient responded rapidly to iodine. On May 17, 1948, his BMR was +3. He has remained well without additional treatment.

Comment. The case demonstrates that hyperthyroidism with exophthalmos may develop following the removal of an actively secreting parathyroid adenoma. The explanation offered for this occurrence is that the overactive parathyroid adenoma had inhibited the hypophysial basophile cells which was reflected in the basal metabolic rate of —16. After removal of the inhibitory influence the basophile cells responded with a temporary overaction to cause the hyperthyroidism and the exophthalmos.

Additional support for the concept that depression of the hypophysial basophile cells may lead to an increase in size of the parathyroid glands is found in a study of Cushing's syndrome (Heinbecker,[12] 1946). In this syndrome an adenoma of the parathyroid gland is not infrequently found. Basophile cell function is considered to be depressed because of the elevated blood cholesterol and decreased metabolic rate found in patients with Cushing's syndrome.

CLINICAL DATA

Prolonged experience with the surgical treatment of hyperthyroidism, together with observations on the specimens removed at operation, permit the deduction that hyperthyroidism may result either from overaction of cells localized in a nodule, or from a diffuse overactive acinar tissue with a varying degree of hypertrophy of the entire thyroid gland. In the first instance, clinical study fails to reveal evidence of a general disturbance of the endocrine balance in such persons. The primary cause of overactivity apparently is local, whereas in the instances where the thyroid gland is generally overactive there is invariably evidence of a generalized disturbance of endocrine balance. This is exhibited, among other things, by an alteration of adrenal gland and sex gland function.

Recent investigations of hyperthyroidism due to an overactive local nodule have been reported by Cope, Rawson and MacArthur[13] (1947). Their demonstration that the thyrotropic hormone is concentrated in the cells of the overactive nodule, leaving the remainder of the thyroid gland relatively inactive, gives excellent support to the belief that the primary alteration is in the involved cells. Their evidence indicates also that the thyrotropic hormone stimulates the secretion of thyroid hormone by the involved cells; in fact, after a fundamental change has occurred in the adenomatous tissue its cells become more than normally responsive to the thyrotropic hormone. Experience with hypophysectomized animals in which marked thyroid atrophy occurs,

indicates that without thyrotropic hormone such altered cells would not continue to be overactive. Demonstration by the authors that radioactive iodine is concentrated in the overactive cells is of fundamental significance. It, too, supports the concept that the hyperthyroidism due to an overactive nodule is not associated with a generalized endocrine imbalance. Only when the primary disturbance is in the central nervous system and of a type which leads to overactivity of the hypophysial basophile cells, with a consequent overproduction of thyrotropic hormone, does the disease become a generalized endocrine disturbance.

Hyperthyroidism is associated also with overaction of the autonomic nerve system "centers" of the hypothalamus. Among the signs and symptoms attributable in part to such action are tremor, tachycardia, irregularities of the pulse, hyperacidity, hypermobility of the intestines, and sweating. These signs may be produced experimentally by excitation of the sympathetic and the parasympathetic nervous systems. They may be seen also as effects of the administration of thyroid substance itself, except for sweating, which is entirely neurogenic in origin. Here, as elsewhere, biologic processes occurring in animals possessing a complex interrelationship between their nervous and endocrine systems may be initiated either by a neurogenic or by a humoral mechanism. Characteristically these mechanisms differ in the speed of their action. Neurogenically initiated effects are rapid in their development, to be supported by the more slowly developing humoral influences.

HYPERFUNCTIONING SINGLE ADENOMA OF THE THYROID

Illustrative Case: A 50-year-old white married housewife (Fig. 7) entered Barnes Hospital because of a constant feeling of increased warmth, increased perspiration, nervousness and tachycardia. She had had a goiter for 15 years. This did not disturb her health until nine years ago, when her toxic symptoms began to manifest themselves.

Examination revealed a well localized nodule in the right lobe of the thyroid; the remainder of the thyroid gland was not enlarged. B. P. 170/70; BMR +31; blood cholesterol 270 mg. per 100 cc. WBC 6470, percentage of circulating lymphocytes, 27.

The patient was treated with radioactive iodine. Her symptomatic response was dramatic, she gaining 20 pounds within seven weeks. Three doses of radioactive iodine totaling 25 millicuries were administered over a seven-month period before the basal metabolism returned to normal. By this time the nodule had reduced itself one third in size.

Comment. The patient was considered to have a single adenoma of the thyroid on the basis of physical examination only. She was chosen to represent the single adenoma group because of her satisfactory response to radioactive iodine. The result would be anticipated from the findings of Cope, Rawson and MacArthur (1947, loc. cit.) which demonstrated that active adenomatous thyroid tissue has an avidity for iodine, almost to the exclusion of less active acinar tissue. The surgical removal of such nodules results in a complete and permanent cure of the patient, a gain indicating that the disease is due to the local disturbance in the thyroid nodule.

GENERALIZED HYPERFUNCTION OF THE THYROID GLAND

Illustrative Case: A 16-year-old white unmarried female (Fig. 7C) entered Barnes Hospital because of nervousness, tachycardia, sweating, increased appetite, unstability and tremor present for six months. Amenorrhoea had been present for three months. A progressively enlarging goiter had been noted for two months.

Examination revealed diffuse enlargement of the thyroid gland. Pulse 110; BP 130/68. The skin was of fine texture and moist. The eyes were prominent, with some lid lag. Marked fine tremor of the fingers was present. WBC 6300; percentage of circulating lymphocytes 50; BMR +36. Plasma cholesterol was 120 mg. per 100 cc.

After treatment with propyl thiouracil and iodine a subtotal thyroidectomy was performed. Three days after operation the patient menstruated normally. She has continued to do so normally. Microscopic study of the thyroid tissue removed showed marked generalized changes which have been found to be characteristic of overactive acinar tissue.

Since operation her symptoms and her exophthalmos have both regressed. Her basal metabolic rate three months after operation was normal.

Comment. The high percentage of circulating lymphocytes is taken to indicate underactivity of the adrenal cortex. Studies of the vaginal mucosa before operation showed changes characteristically seen during active estrogen production. At this time the gonadotropic titer on a 74-hour urine specimen was 1.12 mouse uterus units. On the second day the post-thyroidectomy 24-hour urine specimen contained 6.2 M.U.U. The daily urine content for a 20 to 30 year old regularly menstruating female averages 3 M.U.U.* It is believed that the menstrual period occasioned in the immediate postoperative period was the result of the liberation of a luteinizing factor rather than to an excessive release of follicule stimulating hormone. This would be indicative of a restoration of balance between hypophysial basophiles and eosinophiles, because the latter are the source of the luteinizing hormone.

DISCUSSION

Of crucial importance in the chain of evidence supporting the present concept of the pathogenesis of hyperthyroidism is the demonstration by us that the hypophysial basophile cells secrete a hormone trophic to the thyroid gland. This finding is confirmed by Brolin[15] (1946) who showed that in the rat, proliferation of the thyroid acinar tissue occurs on exposure to cold. In animals so treated a marked increase in the basophile cells of the glandular hypophysis occurs. He showed also that exposure to cold led to an increase in the amount of circulating thyrotropic hormone. Thus, both histologic and functional evidence is available to support adequately the evidence obtained in this laboratory indicating that the basophile cells of the glandular hypophysis are the source of the thyrotropic hormone.

The finding that prolonged administration of posterior pituitary hormone results in an increase of well granulated hypophysial basophile cells affords a mechanism whereby the pathogenesis of hyperthyroidism may be associated with augmented activity in the central nervous system, particularly the hypothalamus. Clinical experience supports such an association. Thus an analysis

* I am indebted to William H. Masters, M.D., for these analyses.

of the signs associated with hyperthyroidism, particularly in Graves' disease, shows that many of them are attributable in part to overactivity of the autonomic nervous system. The hypothalamus appears to be the chief regulating "center" for the control of both the autonomic nervous system and the endocrine system of the body. Clinical experience and the experimental evidence of Bronk, Pitts and Larrabee[16] (1940) indicate that both the sympathetic and the parasympathetic systems can be depressed or augmented in their activity by fibers coming to the hypothalamus from the central nervous system. Its regulating influence on the endocrine system is indicated by the experimental results in the puncture dogs of a marked decrease in basophiles, and the opposite result of an increase in basophiles after the administration to normal dogs of posterior lobe hormone. Depression of the activity of the supraoptic and the paraventricular nuclei which innervate the neural hypophysis results in a decrease in the release of posterior lobe hormone and a decrease in the number of basophiles. The increase in the number of basophiles which follows the administration of posterior lobe hormone indicates that increased activation of the supraoptic and the paraventricular nuclei would result in such an increase of basophiles. The conclusion is warranted that the maturation of the glandular hypophysial basophile cells is under neurogenic control, by way of the neural hypophysis, regulated by fibers from the hypothalamus.

This interpretation is supported adequately by evidence herein presented and also by that of Brolin (1946, loc. cit), who showed that section of the stalk of the hypophysis eliminates the increase of basophiles, and of thyrotropic hormone which follows exposure to cold of the unaltered rat. Therefore, thyrotropic hormone released on exposure to cold is under neurogenic control.

Other experimental conditions pertinent to our problem affecting hypophysial basophile cell maturation are the removal of the thyroid gland or of the ovaries or the testes. It is accepted generally that an increase in the number of basophiles follows removal of the thyroid gland or of the gonads. That the increase of basophiles which appears following these procedures is associated with an increased release of thyrotropic or of gonadotropic hormone has been shown by Addison[17] (1917) by Smith, Severinghaus and Leonard[18] (1933) and by Finnerty, Meyer and Marvin[19] (1944).

Chouke, Friedman and Loeb[21] (1935) showed that in the female guinea pig during the sexual cycle the proliferative activity, and presumably also the metabolic activity of the thyroid acini, is greater than in male animals of corresponding age. It is probable that the mitotic proliferation of the thyroid gland undergoes cycles which are correlated to the sexual cycle, the maximum in mitotic activity being low during the follicular phase. It rises during the lutein phase, reaching the highest point at approximately the fifth day of the cycle in the guinea pig, at a time when the uterine mucosa also reaches a maximum of proliferation.

Experimental and clinical evidence obtained in this laboratory indicates that ordinarily basophile cells are trophic to the ovarian follicles as well as

to the thyroid gland. It follows that conditions which augment thyrotropic hormone may also recognizably increase gonadotropic hormone activity. Following operations in which the thyroid or the gonads alone are removed, such activation need not occur, or if it does, it may be slight for the glands not removed. In hyperthyroidism, as seen in Graves' disease, both hormones apparently are released from the basophile cells.

It has been shown also that any augmentation of estrogen release increases the effect of posterior lobe hormone, particularly of the oxytocic fraction (unpublished data in this laboratory). Sex hormone influences on the central nervous system and on the maturation of the basophile cells of the glandular hypophysis presumably are significant in determining the higher incidence of hyperthyroidism in the female than in the male.

In a previous communication (Heinbecker[20] 1948, loc. cit) it was shown that in the dog, depression of the supraoptic and the paraventricular hypothalamus nuclei affects a change in the cytology of the glandular hypophysis characterized by a preponderance of the eosinophile cells and a marked loss of basophile cells (Fig. 9). Because of this imbalance changes are effected in the function of the other endocrine glands of the heart and of the kidneys, which result in the development of diastolic hypertension, obesity, decreased sugar tolerance, and arteriosclerosis. The incidence of these sequelae, and their severity, vary considerably because of factors not yet understood completely. The differences in bodily reaction to a given change in hormonal secretion, or imbalances between secretions, may be assigned at present only to a "constitutional factor." Essential hypertension is ascribed primarily to the consequences of a functional depression of the hypothalamic nuclei in persons so constituted that their adaptation response to the sum of the exteroceptive and interoceptive influences acting on their central nervous systems is a depression of the supraoptic and the paraventricular nuclei of the hypothalamus. Hyperthyroidism, on the other hand, develops in persons in whom the effect of the sum of the exteroceptive and the interoceptive influences is one of excitation of these same hypothalamic nuclei. From this, basophile, not eosinophile cell preponderance follows, to result in the increased production of hypophysial hormones trophic to the thyroid, the ovarian follicles and the spermatogenic cells. There may be an associated depression of the hypophysial hormones trophic to the adrenal gland and to the progesterone and the androgenic producing cells. The two conditions are, therefore, opposite extremes in the range of variability of activity of the hypothalamic-hypophysial mechanism which serves as the chief regulator of hormonal balance in the body; and which is itself subject to control by the higher levels of the central nervous system.

SUMMARY

Hyperthyroidism results from the release of normal thyroid secretion in excess.

The excess secretion may be derived from a localized adenomatous group of cells within the thyroid gland or from the normal secretory cells of the thyroid gland in general.

The primary disturbance, where localized overactivity exists, rests within the involved cells. The primary exciting disturbance for generalized overactivity comes from the hypophysial basophile cells whose secretion is trophic to the thyroid gland. Overactivity of the hypophysial thyrotrophic cells results primarily from an increase of the secretion of the neural hypophysis which is under nervous control through fibers coming from the supraoptic and the paraventricular hypothalamic nuclei.

Hyperthyroidism caused by increased activity of the normal secretory cells of the thyroid gland in general, occurs in persons so constituted that their adaptation response to the sum of their external and internal body stimuli is excitation of the supraoptic and the paraventricular nuclei.

Depression of the thyroid gland, the ovarian follicles, and the seminiferous tubule cells also increases the maturation of the hypophysial basophile cells by decreasing the normal inhibitory influence of these structures on such maturation.

Fluctuations in hypophysial basophile cell activity occur during puberty, menstruation, pregnancy, and the menopause. Increased estrogen secretion facilitates the action of the secretion of the neural hypophysis. These factors are significant in causing a higher incidence of hyperthyroidism in women than in man.

Exophthalmos, before chronicity is established, is a reversible phenomenon. It results from the swelling of the intra-orbital contents, particularly the muscles, the connective tissue and the fat. An accumulation of lymphoid tissue occurs also. The swelling is a result of water retaining influences of the hormone of the neural hypophysis, and particularly of the thyrotropic hormone. A depression of the thyroid hormone has a similar influence. The lymphoid tissue accumulation is a result of a depression of the adrenal cortical function, associated with the endocrine imbalance tending toward hyperthyroidism. A local susceptibility of the orbital tissue to the water retaining influences of the involved hormones is assumed.

The hypophysial basophile cells are inhibited by an excess of parathyroid hormone. The secretory production of the hypophysial basophile cells is inhibitory to the parathyroid gland. Removal of an actively secreting parathyroid tumor may permit overactivity of the hypophysial basophile cells and the production of hyperthyroidism.

Acknowledgments. I am indebted to Dr. Mather Pfeiffenberger for the exacting work of counting the cells in the glandular hypophyses reported on.

I am grateful to the Eli Lilly Company for the posterior lobe extract in protamine zinc; to the Winthrop Chemical Company for the preloban; to the Armour Laboratories for the thyrotropic hormone; and to the Schering Corporation for the desoxycorticosterone pellets.

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DISCUSSION.—DR. FRANK H. LAHEY, Boston, Mass.: I would not have you feel that from an investigator's point of view I think I am competent to discuss this paper—so informative, interesting, and so valuable in clearing (in my mind) some of our uncertain conceptions of the origin of hyperthyroidism.

On the other hand, many of you may not be as interested as I have been in how and why hyperthyroidism develops. Having literally grown up with it from the stage when we knew next to nothing about it, it is fascinating to see various fundamental facts related to development of this disease each year become better and better revealed, until we now have a well-connected conception of the origin of hyperthyroidism. This paper supplies, for me, some of the links which have been missing up to now.

We have for a number of years known of the interrelationship of the anterior pituitary and its thyrotropic stimulating hormone with hyperplasia of the thyroid and the depressing influence of an increased production of thyroxin on what we thought was the anterior pituitary.

It has been known for a number of years that there are neural pathways between the hypothalamus and the posterior pituitary, but the missing link has been the lack of demonstrable neural pathways connecting the hypothalamus or the posterior pituitary with the anterior pituitary. We now have revealed at least a more complete picture of the origin of this disease which has been so confusing to all of us in the past.

The history of the clarification of many of the beclouded features of hyperthyroidism has been a fascinating one, and this appears to be one of the last links to complete the chain.

In this chain of events blood iodine studies have been extremely interesting, particularly since we have learned to fractionate iodine into its organic and inorganic fractions. We have learned from these studies why certain things happen which we knew happened but previously we did not know how. It was through blood iodine studies, when we began to fractionate iodine, that we were able to demonstrate that the thyroid storms, which we assumed were due to increased outputs of thyroxin, were truly due to this, as could be demonstrated by the marked increase in organic iodine (the hormonal fraction) within two hours after the operation. It was possible to demonstrate that the intake of blood through the artery contained a lower organic iodine fraction than did the output of blood containing the hormonal factor in the veins And now something which we have assumed for a great many years has been demonstrated microscopically by a young South American working at the Massachusetts Institute of Technology, Dr. de Robertis, who by freezing methods and staining has been able to demonstrate the bipolarity of the thyroid acinar cell.

We have known in the past that there have been periods of secretion and rest in the thyroid. We could demonstrate by thyroid involution and distention of the thyroid acini that there were periods of activity, and by the high columnar and crinkled type of epithelial cells that it was hyperactive, but it remained for him to be able to stain the colloid which contains the thyroxin, and to demonstrate its extrusion through the periphery of the cell into the capillaries that run along the external portion of the cell, and so on into the blood stream.

Through his work, too, was revealed the enzymatic process called the peroxidase process in the acinar cells, which may play at least some part in the final synthesis of thyroxin. It is now also possible to be better aware of how thyroxin is probably synthesized, first existing in the thyroid as an iodide, then converted into free iodine and joined with tyrosine to form diiodotyrosine and then synthesized further to the final stage of thyroxin. It is here that this paper of Doctor Heinbecker is so interesting to all of us who have been concerned with thyroid disease over the years. It is the final development of something that we have all known presumably existed; that is, the relationship between the paraventricular and supraoptic nuclei in the hypothalamus and the stimulation of the basophils in the anterior pituitary, thus to produce the hyperplasia, which in turn produces the excess of thyroxin associated with hyperthyroidism.

Finally, I think that perhaps the most valuable development in recent years, for which we owe so much to Astwood, MacKenzie and various others, is the making available of the antithyroid drugs which have literally converted these patients coming to surgery to completely nontoxic states and which have done away completely with the danger of table deaths, postoperative reactions, and all the harrowing events which used to go with surgery of patients still in an intensely toxic state. I would like to tell Doctor Heinbecker how much I have enjoyed listening to this delightful presentation which so helps to clarify a situation that has not been completely clarified before.

DR. WILLARD BARTLETT, JR., St. Louis, Mo. (guest): Let me express my appreciation of the opportunity to speak today, and to congratulate Doctor Heinbecker on his beautiful presentation. I cannot refrain from making a few remarks about exophthalmos which are prompted by some of his statements.

I have repeated in the past, until I am afraid some of you are tired of hearing it, that until one with an exophthalmometer regularly examines the eyes of every patient with a thyroid disorder and records the findings at regular intervals throughout the course of the disorder, whether it be hypothyroidism primarily or hyperthyroidism to start with, it is very hard to evaluate what is happening to the eyes.

I want to assure you that one's impressions from looking at the eyes, as to how much exophthalmos, if any, is present, or whether the eyes are protruding more or are receding as time goes on, are quite worthless. One can measure proptosis only with an exophthalmometer.

It is most deceptive; and, as a matter of fact, the impression one gets that exophthalmos is present or that it is increasing from time to time, is due largely to the width of the palpebral fissure and to the behavior of the lids themselves. I give this to you for what it is worth, those of you who are also seeing these patients frequently.

In 1934, before the Western Surgical Association meeting in St. Louis, I recorded some of the things upon which Doctor Heinbecker has commented today. Those of you who are old hands at thyroid surgery prior to twenty years ago, will recall that postoperative increase in exophthalmos was ordinarily held to be due to persistent or recurrent hyperthyroidism. It was in the late 1920's and early '30s that we had a number of such instances in patients who, to my bewilderment, proved to be hypothyroid after mature study.

In these cases, reported at the Western Surgical Association, it was learned then that restoring them to normal thyroid balance by thyroid feeding resulted in a prompt regression of the exophthalmos in those patients in whom the exophthalmos had been present for very brief periods. In those in whom exophthalmos had been present for months, little regression occurred, and it was postulated at that time that the pathology involved was one of early edema, and lymph edema, as a forerunner of myxedema in the orbital tissues, which was reversible early by thyroid feeding, but which, if allowed to persist, went on to fibrosis, leading to the picture of the orbital contents described by many individuals (among them Doctor Naffziger) who had done various types of operation for decompression of the orbit in late, long-standing exophthalmos.

I throw out also the comment that there is an early increase in proptosis in nearly all patients after thyroidectomy, no matter what their original measurements may be. This I have recorded previously, and it has been confirmed in a perfectly splendid series of studies from the Mayo Clinic, published within the last two or three years, given the Award of the American Goiter Association a couple of years ago. I am sorry I cannot give you the exact reference.

DR. PETER HEINBECKER, St. Louis, Mo.: I wish to thank those who discussed my paper, particularly Doctor Lahey. His favorable attention to this work will expand the attention given to our humble efforts to a much greater degree than he realizes.

I also wish to thank Doctor Pfeiffenberger, Doctor Fischer, and Miss Dennis, fellow workers in my laboratory, for the help they have given me in making these facts available to you.

TRANSMETATARSAL AMPUTATION FOR INFECTION OR GANGRENE IN PATIENTS WITH DIABETES MELLITUS*

LELAND S. MCKITTRICK, M.D., JOHN B. MCKITTRICK, M.D. AND THOMAS S. RISLEY, M.D.

BOSTON, MASSACHUSETTS

FROM THE NEW ENGLAND DEACONESS HOSPITAL.

This might be considered a report of progress in the surgical management of lesions of the lower extremities in patients with diabetes mellitus. Fifteen years ago in a paper before this Association, one of us[1] in analyzing the deaths following amputations for gangrene, pointed out that the mortality rate was 13.7 per cent; that about 10 per cent of these patients died as the result of uncontrolled sepsis; that if and when some mechanism other than surgery was developed for the control of infection, we might anticipate a mortality following major amputation of about 5 per cent.

Chemotherapeutic agents and the antibiotics have made it possible to control invasive infection, and the mortality rate has fallen as anticipated (Table I). This is of particular significance in the management of these patients with diabetes mellitus, because this control of invasive infection invited a different approach to a selected group of cases. With the danger of ascending infection and septicemia eliminated, it might now be practical to consider each foot on the basis of its arterial supply. In selected cases, amputation might now be performed at a more distal level with safety and a reasonable chance of success. There was reason to believe that if all or part of the toe was gangrenous, amputation through the foot just proximal to the heads of the metatarsals would be more likely to succeed than removal of the toe alone. Such an amputation would, in addition, offer the patient protection against subsequent involvement of the remaining toes, and would give him a useful foot.

In 1944 we did our first transmetatarsal amputation for gangrene of a toe in a diabetic patient. The lesion in this patient was one for which we had previously considered amputation through or above the mid-lower leg as the operation of choice. The operative wound healed promptly. There have been 215 such amputations done at the New England Deaconess Hospital up to January, 1949,† and sufficient time has elapsed to permit a study of these cases in an attempt more clearly to delineate the indications and the technic, and to review the early and late results.

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* Read before the American Surgical Association, St. Louis, Mo., April 22, 1949.

† We are indebted to Drs. T. C. Pratt and C. C. Franseen for permission to include patients operated upon by them and for their cooperation in obtaining follow-up data on their patients.

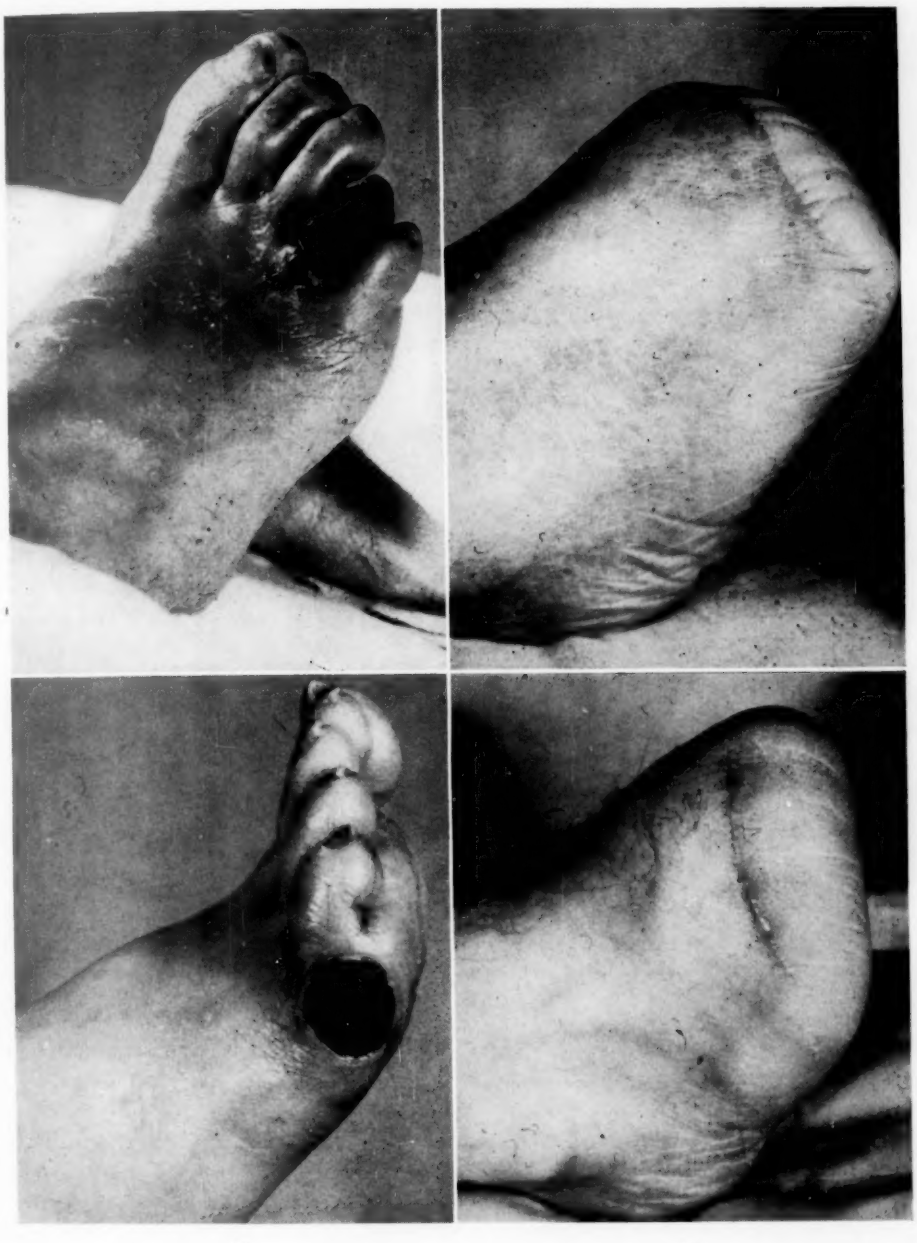


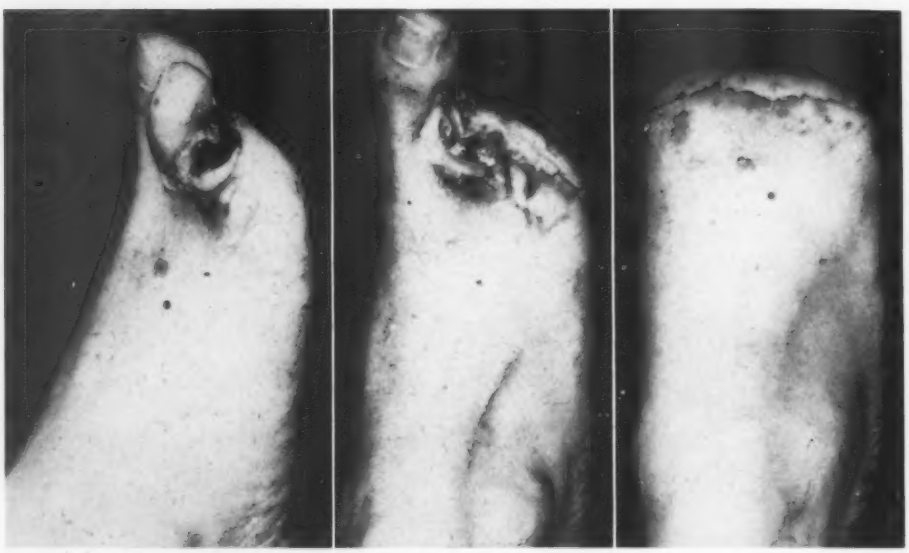
FIG 1.—Gangrene of toe (A) and lateral aspect of base of fifth toe (C). Successful transmetatarsal amputation in these two patients (B & D)

INDICATION

Our experience will permit only a discussion of the anatomical indications. Removal of a toe, especially the great toe, with its metatarsal head, alters weight bearing and increases the vulnerability of the remaining toes; therefore, we prefer the relative security of the transmetatarsal amputation. Factual

TABLE I.—*Mortality Following Major Amputations 1923–1949, New England Deaconess Hospital*

Period	No. Cases	No. Deaths	Mortality (%)
1923–1941	680	93	13.7
1941–1949	358	20	5.5



A B C

FIG. 2.—Exemplifying total excision of open wound and primary closure of transmetatarsal amputation: (A) Initial lesion; (B) local excision of initial lesion and drainage of soft tissue infection; (C) hospital result 18 days post transmetatarsal amputation.

evidence to support this preference is not at hand but, with this thought in mind, we have advised this procedure for the following indications:

1. Gangrene of all or part of one or more toes, providing that the gangrene and accompanying infection *have become stabilized* and the gangrene has not involved the dorsal or plantar aspect of the foot (Fig. 1).

2. A stabilized infection or open wound involving the distal portion of the foot, when total excision of the infected area with primary or delayed closure can be accomplished (Fig. 2).

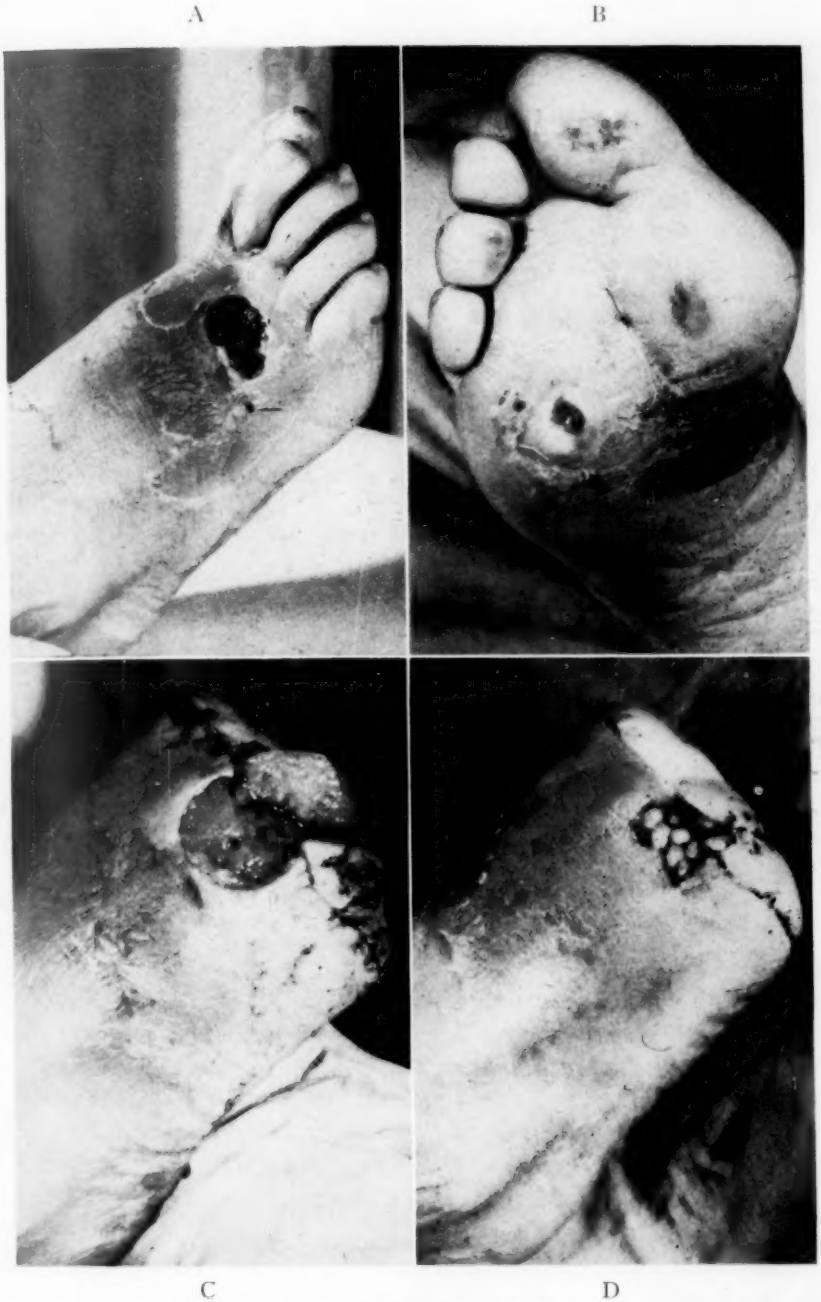


FIG. 3.—Neurogenic foot with destruction of third and fourth metatarsophalangeal joints. Partially closed amputation with subsequent secondary closure of plantar flap and pinch grafts to dorsum. Area of anesthesia totally excised: (A) and (B) presenting lesion; (C) transmetatarsal amputation; area of local infection left open; (D) delayed suture of plantar defect and pinch grafts to dorsal granulating wound nine days post-amputation.

3. An open, infected lesion in a neurogenic foot (a) as a curative procedure when the entire area of anesthesia can be excised (Fig. 3), or (b) as a delaying procedure when the area of infection can be excised but the line of incision is through the area of anesthesia (Fig. 4).

GANGRENE

We know of no way to determine accurately that a transmetatarsal amputation will be successful in a foot whose arterial blood supply is deficient. If the process is stabilized, and if gangrene and infection are well demarcated, there is a borderline group where only trial and error will give the final

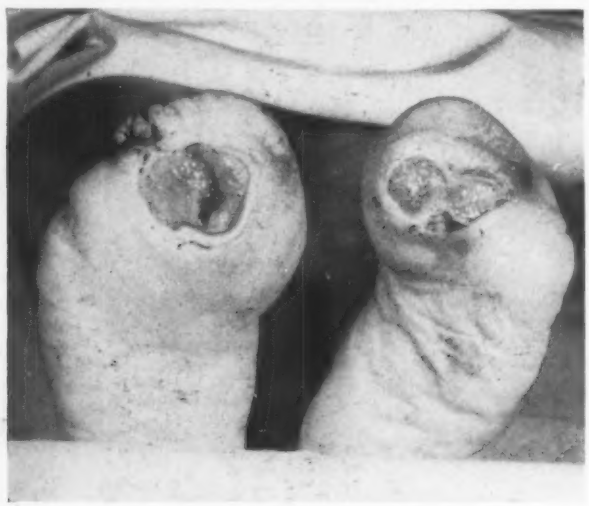


FIG. 4.—Recurrent ulceration on amputation stumps in anesthetic plantar flap. Good circulation and diabetic neuropathy.

answer. With experience we become increasingly accurate in the estimation of the potentialities of the circulation of a given foot, but we are not able always to foretell the outcome with accuracy. We are sometimes pleasantly surprised to obtain early and prompt healing (Fig. 5), just as we are occasionally disappointed to find necrosis and delayed healing or failure to heal (Fig. 6). If the gangrene has extended onto the dorsal or plantar aspect of the foot, only rarely will this procedure be successful. Occasionally an area of gangrene may extend slightly onto the medial or latter aspect of the foot and can be excised without jeopardizing the result (Fig. 1). On the other hand, when the circulation in the foot is adequate, infection may extend well onto the foot and not contradindicate the operation (Fig. 3).

Excision of area of infection. One of the most satisfactory by-products of this operation for gangrene has been its adaptation to a group of patients where the circulation in the foot has been reasonably good, but where the pre-

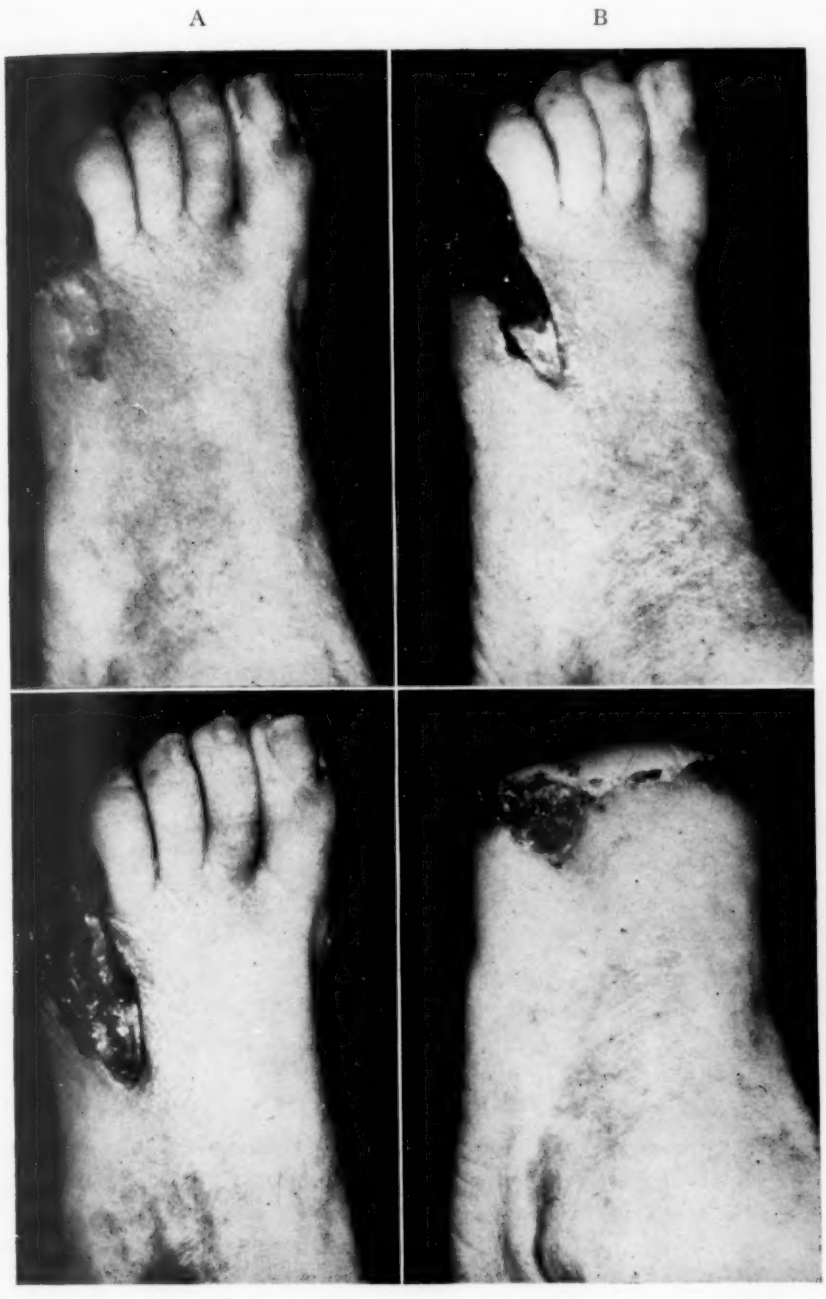
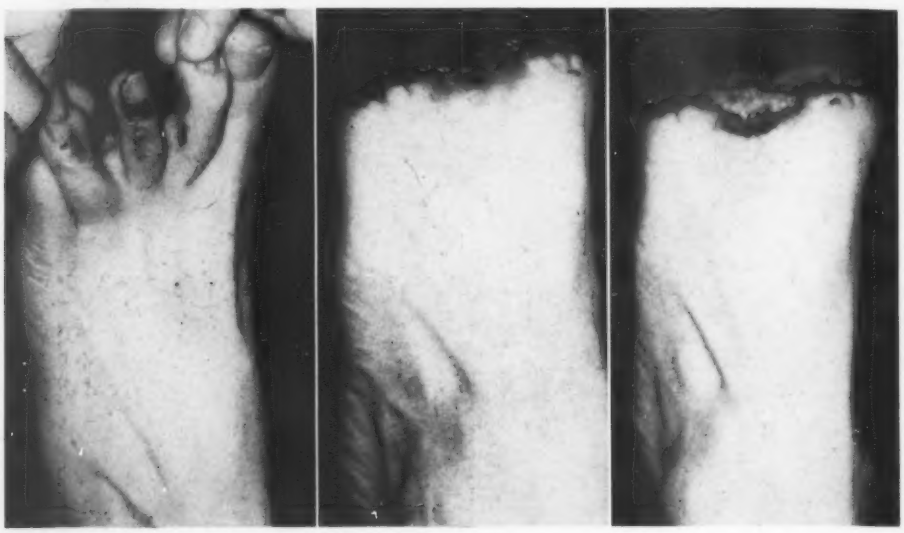


FIG. 5.—Successful transmetatarsal on an extremity with very poor circulation. A failure was anticipated. (A) presenting lesion showing gangrene of the fifth toe, ulceration onto dorsum with diffuse, surrounding cellular reaction; (B) and (C) progressive localization and demarcation; (D) hospital result 21 days post-amputation. The defect on the dorsum is not yet healed.

dominant factor has been infection. We have now had a modest number of patients who entered the hospital with severe local infection, usually involving one of the metatarsophalangeal joints and not infrequently the web space. Initial drainage with or without amputation of one or more toes has been carried out in order to control the infection. After the process has become stabilized it has been possible to do a transmetatarsal amputation, excising the entire granulating area. The edges of the newly made wound are carefully approximated with steel wire (Fig. 2). In a few of these cases a small segment of the wound has been packed loosely with gauze and allowed to heal by secondary intention. In others, a granulating area on the dorsum of the foot has then been covered with pinch grafts removed from the amputated segment (Fig. 7).



A B C

FIG. 6.—Immediate failure in a patient with poor circulation but in whom a successful result was anticipated. (A) presenting lesion; (B) and (C) progressive dorsal necrosis within 12 days postoperatively. Supracondylar amputation done three days after (C).

Neurogenic lesion. These lesions are the most disturbing and baffling of all of the lesions that we see in this group of patients. In most instances there is an open, infected area on the plantar aspect of the foot, surrounded by an area of thick callus, and frequently leading into a metatarsophalangeal joint. There is partial or complete anesthesia to pin prick in the involved area. The arterial supply is usually adequate. A variety of surgical procedures has been utilized for this condition and healing is usually prompt. In almost all instances, however, there will be recurrence in spite of any precaution we have been able to take, unless all of the anesthetic area on the plantar aspect of the foot can be excised. If the incision on the plantar aspect is through skin

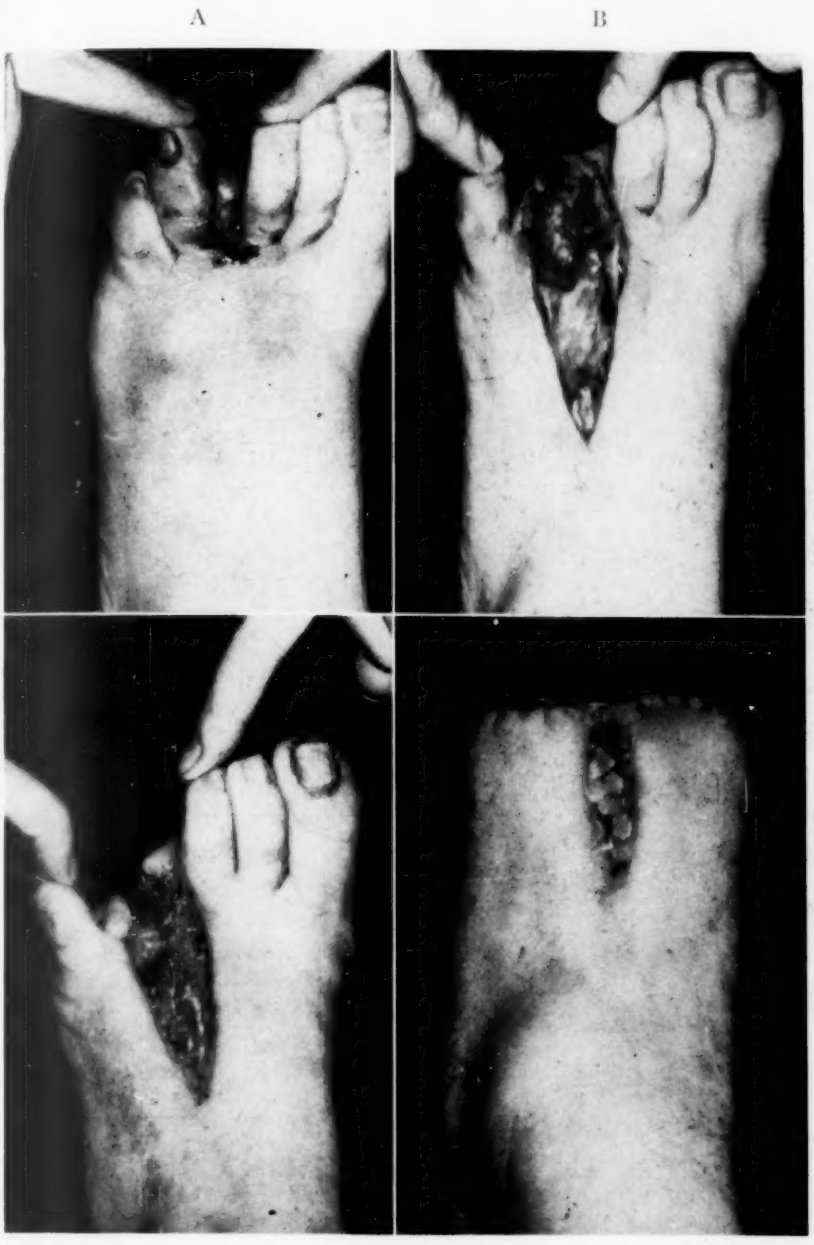


FIG. 7.—An example of preliminary drainage of infection followed in 23 days by closed transmetatarsal amputation. The pinch grafts were taken from the amputated forefoot. (A) presenting lesion; (B) preliminary drainage; (C) stabilized, open wound immediately pre-amputation; (D) hospital result 10 days post-amputation.

with normal sensation, not only will healing be complete, but a good result may be expected. Otherwise, almost without exception, the result will be merely a delaying one (Figs. 3 and 4).

PREPARATION FOR OPERATION

Probably the most important single factor favoring a successful outcome in a patient with borderline circulation is selection of the proper time for operation. Just when this is we are not certain; but every effort should be made to do the operation after the gangrene and infection have demarcated. We know from past experience that patients entering the hospital with severe pain will continue to benefit from the hospital routine for a period of two to three weeks. We have, therefore, taken approximately three weeks as the period during which adjustment of the local circulation may be expected to take place. Maximum improvement should then be evident and the patient ready for operation. Patients are given penicillin, usually a preparation of procaine penicillin G, 300,000 units once or twice daily if infection is present in association with the area of gangrene. When infection has been controlled, usually in five to seven days, penicillin is stopped. Buerger exercises are started and continued for approximately two weeks. Patients with more favorable circulation may be operated upon at an earlier time. During this period of preparation the general condition of the patient is supported; transfusions of blood are given to obtain a hemoglobin of 13 Gm. or more; the diabetes is adjusted and every effort is made to have both the patient and the local area in the best possible condition for operation. During the 24 hours before the time of operation, the patient is given 600,000 units of the procaine penicillin G. This is continued for four days postoperatively.

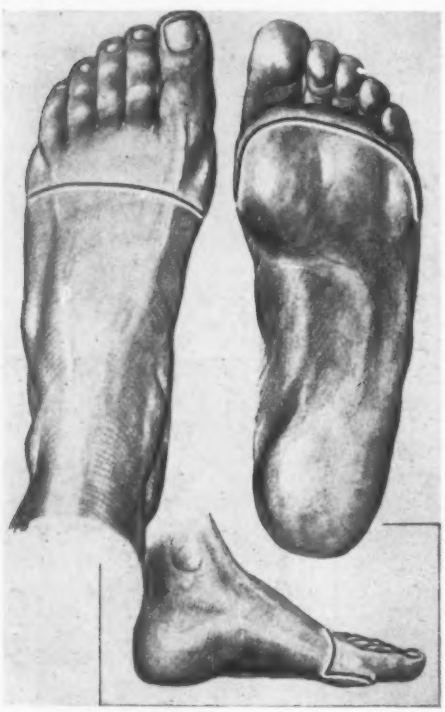


FIG. 8.—Illustration showing line of incision. Note long plantar flap.

TECHNIC OF OPERATION

A low spinal anesthesia has been used for all of these operations. The lines of incision are shown in Figure 8. The long plantar flap is important because experience has shown that the blood supply to this flap is much better

than that to the dorsal flap. Great care is taken to make the incisions decisive, using a sharp knife which is changed after the skin incision has been made. There is no undermining or dissection of the dorsal flap, but the incision is carried directly down to the bone. Dissection of the plantar flap is kept close to the underlying bone. Each metatarsal is divided just proximal to its head with bone forceps. All sesamoid bones are removed. No special attention is given to the tendons. Careful hemostasis with a minimum of trauma is essential. Closure is carried out in one layer using a serum proof suture material to approximate the skin edges. Fine (No. 38) stainless steel wire has proved the most satisfactory in our hands. Closure of the wound is started from each end, to insure accurate approximation at these two vulnerable areas. There must be no tension to the suture line, nor should the flaps be redundant. The wound is not drained.

POSTOPERATIVE CARE

An important feature of the postoperative, as well as the preoperative care is the position of the patient in bed. In order that the extremity not be blanched and the veins remain full, the head of the bed is elevated so that the heart is always at a slightly higher level than the most distal portion of the feet. This dependency may be accomplished either by placing shock blocks under the head of the bed or by cranking the head of the bed up to the desired level.

Patients are kept on bed rest in the above fashion for a period of two to two and a half weeks after amputation. One half the stitches are removed about the ninth day, and the remainder between the twelfth and fourteenth day. In preparation for ambulation Buerger exercises are started ten to 15 days postoperatively. Mobilization is begun gradually, starting with one minute three times a day, Buerger exercises are continued, and the amount of walking permitted is gradually increased. Usually the patient is ready for discharge from the hospital three to four weeks after operation. The average postoperative stay for the entire group has been 30 days.

HOSPITAL RESULTS

A total of 215 patients have been operated upon up to January 1, 1949, (Table II). There were two hospital deaths, a mortality of 0.9 per cent. Healing was complete in 155 patients at the time of discharge. Sixty patients failed to heal, and of this group, re-amputation was done at a higher level in 27 patients, with prompt healing in all but one. This latter patient represents one of the fatalities. Thirty-three patients left the hospital with wounds not completely healed.

Fatal Cases. Both patients died of coronary thrombosis. One was a 77-year-old diabetic of 12 years' duration who died on his 48th hospital day, ten days after his transmetatarsal amputation. Preceding the amputation a prostatectomy had been done for urinary retention. The second, a 71-year-old

woman, who had diabetes for 24 years, died on the 24th hospital day. An unsuccessful transmetatarsal amputation had been followed by a supracondylar amputation ten days before death.

Failures. Supracondylar amputation had been advised for five of this group of 27 patients. All of these patients developed early progressive necrosis along the suture line. Most of them had severe local pain in association with the necrosis.

TABLE II.—*Hospital Results Following Transmetatarsal Amputation*

Indication for Operation	Cases	Healed	Unhealed	Re-amputation	Died
Gangrene	145	94	25	26	2
Excision of Infection (neuropathy)	55	46	8	1	0
Excision of Infection	15	15	0	0	0
Total	215	155	33	27	2

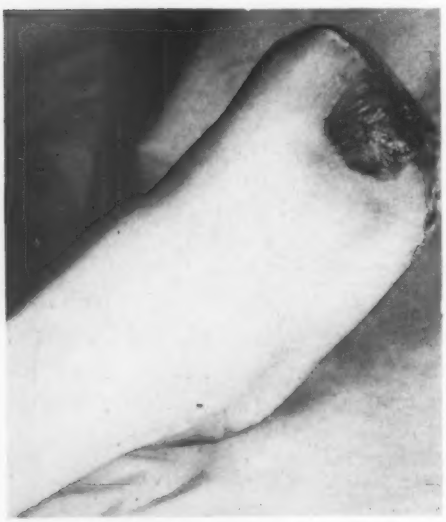


FIG. 9.—Typical dorsal flap necrosis. Subsequent surgical revision was done three and one-half months later with primary healing.

Careful review of the available data does not indicate how a more accurate decision might have been reached. In each case failure was apparently due to arterial insufficiency. A possible exception was a patient with excellent collateral circulation but with no pulsations noted below the level of the femoral artery. This patient was sensitive to penicillin, and is the only patient in the entire series who was operated upon without the protection which this would have afforded. He is also the only patient in this series who developed invasive infection. It was our belief that penicillin would have permitted healing per primum. Rest pain was present in 47.5 per cent of these patients in contrast to 18.1 per cent of the remaining 188. When rest pain does not entirely disappear during the period of preparation, the prognosis is very poor.

Local Complications. Fifty-three patients in addition to those already discussed, did not heal per primum. Twenty of these were healed at the time of discharge from the hospital. Eight of these patients had a minor separation of skin edges. In the remaining 12 patients, partial primary closure of the wound was followed by secondary suture, skin grafting, or healing by second intention.

The most important local complication in this group of patients was the development of a triangular area of discoloration on the dorsal flap (Fig. 9) which occurs within 10 or 12 days after operation. In many instances this was transient and did not interfere with primary healing. In 33 patients, the discoloration progressed to necrosis of a segment of the dorsal flap, which involved the skin and subcutaneous fat, and which had not healed at the time of discharge from the hospital. If this necrosis is not too extensive, and if it demarcates early, there will be gradual separation of the necrotic tissue. This may take many months, during which time the patient is up and about. In selected cases, after complete separation of the slough, the defect may be closed by excision of the open area, shortening of the underlying metatarsal shaft or shafts, and careful approximation of the skin edges.

LATE RESULTS

Anatomical. One hundred and fifty-five patients left the hospital with their stumps completely healed. We have been unable to learn the present condition

TABLE III.—*Late Results Following Transmetatarsal Amputation; Stumps Healed at Time of Discharge*

Indication	Cases	Recurrent Ulceration	Re-amputation
Gangrene	88	10	6
Excision of infection (neuropathy)	43	14	1
Excision of infection	15	0	0
Total	146	24	7

of nine of these patients. Twenty-four, or 16 per cent of the remaining 146, have had subsequent trouble (Table III). In ten of these patients the amputation had been done for gangrene. Three of these have developed a small area of necrosis at the medial or lateral corner of the scar. A fourth has a painful fissure of the heel. Six patients have survived successful amputation at a higher level necessitated by further gangrene. These six patients all had useful limbs for a minimum of one year (average 18.7 months). In the neuropathic group 14 patients have recurrent ulcerations at a weight-bearing point. One developed a callus and ulceration underlying a bony spur which developed at the transected end of the second metatarsal. This patient was well three months after excision of the spur. Re-amputation was necessary in one patient in this group, a 31-year-old diabetic with excellent circulation. He remained well for one year, then recurrent ulceration and intractable infection resulted in higher amputation.

Thirty-three patients left the hospital with the stump unhealed. Four of these healed in from two to ten months, but their present condition is unknown. Of the remaining 29 patients (Table IV) 13 have subsequently

healed. Five of these had a successful revision of their stump (original amputation for gangrene) and in eight, healing has taken place by secondary intention. In six of the ten patients who remain unhealed the appearance of the local lesion would suggest that ultimate healing and a satisfactory result should occur. In the six patients who have been re-admitted to the hospital and survived amputation at a higher level the intervals between the two amputations have varied from two to ten months. At no time did healing take place in this group.

Functional Results. We can only report upon the function of the transmetatarsal stump as it pertains to this elderly group of people (average age 61.5 years) whose physical activities are of necessity somewhat limited. No patient considered his or her activities to be limited because of the loss of the distal portion of the foot. There is a lack of forward balance. Some patients report that in walking at a rapid pace the foot tires more easily than formerly. All patients walk without a limp. Those with bilateral transmetatarsal stumps (19 patients) use a shortened stride. In all cases this stump has fully met the daily requirements of this group of patients and we feel justified in classifying the functional results as "excellent."

TABLE IV.—*Late Results Following Transmetatarsal Amputations, Stumps Unhealed at Time of Discharge*

Indication	Cases	Healed	Unhealed	Re-amputation
Gangrene	22	8	8	6
Excision of infection (neuropathy)	7	5	2	0
Excision of infection	0	0	0	0
Total	29	13	10	6

Prosthesis. With but few exceptions these patients have been discharged from the hospital without any special type of shoe. The toe of the shoe of the amputated foot has been filled with lamb's wool to lessen the tendency of the shortened foot to slip forward.

Three patients with unilateral transmetatarsal amputations have had special inner soles made and report that they are very satisfactory. This inner sole consists of a flexible steel plate with the space which the forefoot would have occupied filled with rubber foam. This inner sole is not unlike that described by Bates.[2] It has given comfort to the end of the amputation and has stiffened the sole, both of which are important features. From this very limited experience it would seem to us that perhaps this may be the simplest and most satisfactory appliance.

Five other patients with unilateral amputations have had a short, narrow, flexible steel plate inserted between the outer and inner sole of the regular shoe. This steel plate extends to the level of the transected metatarsals, and minimizes the annoyance resulting from the flail-like action of the distal,

empty portion of the shoe. This seems a more expensive way to handle the problem and probably no more satisfactory than a well-constructed inner sole. One ingenious patient with a unilateral amputation, a retired cobbler, simply had a cobbler friend do what amounted to a transmetatarsal amputation of his old shoe. This, he says, has been perfectly satisfactory.

All of the patients with bilateral amputations use custom-made short shoes. None of this group has used a shoe of the old size with specially constructed inner soles as described above. It is possible that such a solution would be satisfactory, and if so, the expense of having special shoes made each time a new pair is required would be eliminated. We are impressed that so few of these patients have felt the need for custom-made shoes.

TABLE V.—*Summary of Results*

	Cases	% Total	Follow-up (Months) Av.	Max.	Min.
Satisfactory*	135	67	28.5	57	7
Unsatisfactory†	32	16	20.8	56	4
Failures‡	35	17	....	..	..
Total	202	100	....	..	..

*Nineteen patients died at intervals of 8 to 54 months after discharge from the hospital of conditions not related to the amputation.

†Four patients died at intervals of 14 to 35 months after discharge from the hospital of conditions not related to the amputation.

‡Includes the 2 operative deaths.

Summary of Results. If healing has been complete and the amputation stump does not limit the patient's activities, we have classified the result as "satisfactory." If complete healing has not taken place, or if there has been recurrent trouble in relation to the stump but the patient is ambulatory, we have considered the result "unsatisfactory." If healing did not occur, and the open area has progressed resulting in amputation at a higher level, we have called this result a "failure."

The present condition of 202 patients is known (Table V). Thirty-five, or 17 per cent, of these (including the two who died) are failures. Thirty-two (16 per cent) have had one or more of a variety of local symptoms, but still retain limited use of their extremities. These we have considered as unsatisfactory. We feel that the remaining 135 patients, or 67 per cent of the entire group whose present condition is known, have had satisfactory results following their transmetatarsal amputations.

SUMMARY

1. Two hundred and fifteen transmetatarsal amputations have been done from July, 1944, to January 1, 1949, with two hospital deaths, both due to coronary thrombosis.

2. Thirty-three of these failed to heal, and came to amputation at a higher level.

3. The present condition of the remaining 174 patients who left the hospital with a transmetatarsal amputation is known. One hundred and thirty-five of these are completely satisfactory. In 32 patients the end result is still undetermined and is regarded as unsatisfactory. Seven patients have come to higher amputation after complete healing for a minimum of one year.

4. The functional result has been excellent in all successful cases. Most patients with unilateral amputations use lamb's wool in the toe of their own shoe. Three patients use an inner sole insert with a rubber toe, which is probably the best, and five patients use a flexible steel bar between the outer and inner sole.

5. Custom-made short shoes are used by all patients with bilateral amputations, and this is regarded as a satisfactory solution.

6. We consider the results very gratifying, and believe amputation at this level to be a major contribution to the management of this group of patients.

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DISCUSSION.—DR. LOUIS G. HERRMANN, Cincinnati, Ohio: At the Cincinnati General Hospital we have employed, since 1934, the various conservative amputations through the foot for gangrene of the toes due either to arterial disease or to infection. We agree with Doctor McKittrick and his associates that many lives and many limbs can be saved by such procedures, but we differ with them slightly on certain technical aspects of the operation. It has been our experience that the transmetatarsal amputation gives the most serviceable stump of any of the amputations through the foot. We have allowed the end of the stump to remain open until a healthy granulation tissue base developed, then secondarily closed it by split thickness skin grafts, rather than make large skin flaps and close the stump at the primary operation. In patients without arterial insufficiency, the primary closure of the stump can usually be done safely.

Doctor Furste and I published the end-results of transmetatarsal amputations in 91 patients who were subjected to this procedure between 1934 and 1947. Of these patients, 37 per cent obtained an excellent or good result and a useful weight-bearing foot.

The antibiotics and chemotherapeutic agents have enabled us to control local infection so our future series should present an even higher percentage of useful weight-bearing feet after transmetatarsal amputations. Doctor McKittrick has demonstrated the value of conservative amputation in the diabetic patient and we are in agreement that these operations should be performed more frequently in patients with localized gangrene of the toes

DR. MICHAEL E. DEBAKEY, Houston, Texas: I should like first to express my grateful appreciation to Doctor McKittrick and his associates for directing our attention to this valuable procedure. There are two facts that are particularly impressive in emphasizing the value of this procedure; first is the salvage of functioning extremities, and second is the strikingly low mortality. Those of us who have long been interested in peripheral vascular disease can fully appreciate the great improvement in both mortality

and morbidity which has been achieved by Doctor McKittrick and his associates, particularly in this older age group of patients with diabetes. Only about ten years ago the case fatality rate in the surgical management of such cases was as high as 30 to 40 per cent, with emphasis being placed on amputation above the knee. In striking contrast with these results Doctor McKittrick and his associates reported a case fatality rate of about one per cent. In addition, the patients were given functioning extremities. Thus, they have literally attained the salvage of both life and limb.

On the basis of our experience with this problem, there are two questions I should like to ask Doctor McKittrick. First, were there any differences in the results obtained between the diabetic and the non-diabetic group of patients with arteriosclerosis? I raise this question because in our experience it was observed that, if anything, somewhat better results may be obtained in the diabetics so long as the diabetes is properly controlled.

Secondly, I would like to ask what experience have they had in combining this procedure with sympathectomy. In our experience, sympathectomy has appeared to be a valuable adjunct in the treatment of this particular group of patients. By employing sympathectomy as a preliminary procedure it has been possible in some instances to avoid transmetatarsal amputation. We have been gratified to observe that following sympathectomy in many of these patients with localized gangrenous processes, such as those shown in some of Doctor McKittrick's slides, sufficient improvement in the circulation may take place for the process to be arrested with complete healing and with a minimal loss of tissue, thus precluding the necessity of subsequent amputation, either at the transmetatarsal level or higher. In a series of 32 cases of this kind treated in this manner and followed from six months to four years, amputation was completely avoided in 50 per cent.

Dr. Reginald H. Smithwick, Boston, Mass.: As Doctor McKittrick and his associates have indicated, the advent of chemotherapy and antibiotics have made it possible to consider conservative amputations in increasing numbers of patients. The degree of success which they have had is most impressive to me, and should stimulate a widespread interest in reducing the number of major amputations which are being performed in the presence of localized ulceration and gangrene in patients with peripheral vascular disease.

Valuable as chemotherapeutic agents and antibiotics may be, other factors also are of great importance in determining the outcome of conservative amputations of toes or portions of the foot, particularly when extensive main vessel obliteration is present.

The first essential is that the collateral circulation be adequate for healing. There is no absolutely certain way to determine this, but I have found the following simple rules of thumb to be quite reliable: First, if the temperature of the skin at the site of amputation is 75 degrees Fahrenheit or more after exposure of the extremities to a room temperature of 68 degrees Fahrenheit for one hour, one can be reasonably certain that an adequate blood flow exists. Secondly, when, after blanching of the foot on elevation, flushing in the dependent position begins in twenty seconds or less, in all probability the collateral circulation is adequate. If evidence of an active vasoconstrictor mechanism is detected by appropriate studies, it is advisable to sympathectomize the extremity as a preliminary measure.

If adequate circulation seems to be present, one then comes to the actual operative procedure. Particularly when one is contemplating a closed amputation, the preparation of the operative field is of great importance. This requires a very careful walling off of the ulcerating or gangrenous areas, with meticulous preparation of the skin with soap and water, using cotton or some non-traumatizing substance for this purpose. Recent experiences with Phisoderm and G-11 suggest that this may be of great value in the preparation of the skin. This is a most important part of the operation, and should be done by the surgeon himself.

The actual technic of amputation is of great importance. The skin flaps must be fashioned without trauma or handling of the tissues with toothed forceps or other irritating instruments. No unnecessary undercutting of flaps is permissible. There must be no dead space. The skin must be approximated without tension, placing the sutures so as to obtain perfect approximation without gaping of fat between them, and tied so as not to obstruct the circulation. The margin between success and failure may be very slight, and for this reason I wish to emphasize these fundamental points, because I know from experience that unless they are more fully appreciated the percentage of success will be low.

In addition to transmetatarsal amputations, at times one may consider the amputation of a single toe either through the proximal phalanx or the metatarsal level. If the remaining toes are rigid and the circulation questionable, the transmetatarsal procedure is preferable. These amputations may be carried out through any portion of the metatarsal bones, and more recently I have found that a very useful foot results from amputations through the distal portion of the tarsal bones. In general, I make the skin flaps where I feel the circulation is adequate, and section the bone at whatever level is necessary to insure perfect approximation of the flaps.

I feel that Doctor McKittrick and his associates are to be congratulated on this excellent presentation.

DR. LELAND S. MCKITTRICK, Boston, Mass.: I want to thank the discussers for adding and contributing so much to this discussion because all of the points brought out are very important. Doctor Smithwick and Doctor Herrmann brought out the fact that technic cannot be over-emphasized. The operation must be carefully done, with great attention to detail, or, as Doctor Smithwick has pointed out, the results will not be good.

We have not tried the skin graft. That is a fascinating approach. We have closed them all, except those wherein we delayed closure. We disregard the tendons. We close the skin with the greatest of care, using fine wire sutures. We have used this on both diabetics and non-diabetics, in reply to Doctor DeBakey's question, but most of our patients have been diabetics.

We have used sympathectomy in a limited number of patients. We feel that there is a group, just as Doctor DeBakey has pointed out, for whom sympathectomy may be the means of avoiding operation, or of adding to the security of amputation. In that patient with the defect shown on the slide, who had had a previous sympathectomy, closure might not have succeeded had it not been used.

I would like to re-emphasize one point. Doctor Smithwick has said that the margin of safety is small. Whether the procedure succeeds or fails in this group with borderline circulation will depend upon the care and preparation of the patient, the judgment and selection of the proper time to do the operation, and the care with which the technic is carried out. The selection of the proper time for this operation probably is the most important single factor in its success.

RECURRENCE OF GASTRIC ULCER AFTER COMPLETE VAGOTOMY*

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DIVISION OF THE VAGUS NERVE supply to the stomach has been performed on 521 patients at The University of Chicago Clinics during the six year period from January, 1943, to January, 1949. In only 20 patients was the operation done for the treatment of gastric ulcer. Because the chief problem in gastric ulcer is the possibility of cancer, subtotal resection was performed whenever the lesion would permit its removal with a sufficient margin of normal tissue to have some significance as a therapeutic measure, should subsequent microscopic study show the presence of carcinoma. Total gastrectomy was not considered wise in the absence of proved cancer. Vagotomy was thus a substitute for a partial gastrectomy which would either not remove the lesion at all or be inadequate in the presence of carcinoma. A number refused gastrectomy altogether but were willing to have the less mutilating vagotomy. A report of the first eight patients was made two years ago[1] and the problem is now reconsidered because subsequent experience has produced some modifications in our views. It is now clear that vagotomy is not as effective in gastric ulcers as we have found it to be in duodenal and gastrojejunal ulcers. We have not yet encountered a duodenal ulcer that has failed to heal or has recurred when the vagotomy has been complete as determined by repeated physiological tests. Failures have been observed, but these have all occurred after incomplete vagotomy in patients where a positive gastric secretory response to insulin hypoglycemia has been obtained on repeated testing, and the nocturnal hypersecretion has not been reduced.

Of the group of 20 patients with gastric ulcers, 17 had vagotomy alone, two vagotomy plus gastroenterostomy, and one vagotomy plus partial gastrectomy. At the present time 11 of these patients are entirely free of symptoms on an unrestricted diet and without medication. One died at home two months after operation, of a cerebral hemorrhage; autopsy was not secured, so the status of the ulcer is undetermined. One patient died of a brain tumor five months after operation. Autopsy in this case revealed that the gastric ulcer had healed. One patient had a vagotomy plus a wedge resection of the ulcer on the lesser curvature. Gastroenterostomy was subsequently performed because of obstructive symptoms, and the patient died from a transfusion

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reaction due to mis-matched blood. In one patient the diagnosis of a gastric ulcer on the lesser curvature was based on roentgenogram findings. Vagotomy was performed, although at the time the surgeon could not be certain of the presence of an ulcer. Symptoms persisted, together with positive roentgen ray findings, and 19 months later a sub-total gastrectomy was performed. No ulcer was found in the resected specimen, and inspection of the short cardiac segment also failed to disclose an ulcer. Persistence of symptoms after the resection indicates that the original diagnosis was in error, and that the patient never had an ulcer. One patient had a severe hemorrhage from a large gastric ulcer on the lesser curvature six weeks after vagotomy. The ulcer was later excised and the patient is well at the present time. Four patients continued to have ulcer distress 4 months, 5½ months, 13 months and 22 months after vagotomy. The first three of these patients submitted to sub-total gastrectomy, and in each case an unhealed gastric ulcer was found in the resected specimen.

It is thus apparent that in at least five of the 20 patients with gastric ulcers, vagotomy failed to bring about the symptomatic relief and objective evidence of healing usually observed following this operation in duodenal and gastrojejunal lesions. In three of the five patients the vagotomy was complete, as evidenced by persistently negative responses to insulin hypoglycemia, together with a satisfactory reduction in the output of acid from the fasting stomach. Summaries of these cases follow.

A. N., a 66-year-old housewife, was hospitalized in October, 1947, with the complaint of typical abdominal distress for the previous four months. She had had one tarry stool three months previously and had had some episodes of vomiting but no hematemesis. There had been a progressive anorexia, with a 30-pound weight loss. In September, 1947, roentgenograms revealed a very large penetrating ulcer on the lesser curvature of the proximal third of the body of the stomach. This measured approximately 2½ cm. in diameter. Nocturnal secretion measured 415 cc., with a free acid of 36 clinical units. On October 17, 1947, exploratory laparotomy was performed and a large penetrating ulcer adherent to the liver was found on the lesser curvature of the stomach near the cardia. An abdominal vagotomy was performed. She made an uneventful recovery and was discharged on the twelfth postoperative day. She was readmitted on November 30, 1947, because of recurrent hematemeses during the previous two weeks, so that she became progressively weak, and had anorexia and recurrent severe vomiting episodes. On the day of admission she was exsanguinated and in a state of impending shock. Supportive measures were instituted, but the hemorrhage persisted intermittently, and on the ninth of December the abdomen was reopened and the ulcer excised locally. The patient recovered, following a stormy postoperative course, and was discharged from the hospital on January 16, 1948. On January 4, 1948, gastric secretory studies were made, and a night secretion varying from 420 to 750 cc., with 25 to 57 units of free acid, was obtained, this despite the fact that there was a large food residue. The insulin test was also interpreted as being probably positive. Roentgen ray examination in January, 1948, revealed a marked deformity of the mid-portion of the stomach with a narrow channel connecting the two portions, and there was marked gastric retention. The patient's subsequent course has been remarkably uneventful. She has gained 27 pounds to February, 1949, and was eating everything without distress. Further roentgen ray examination of the stomach has not been made.

T. B., a 50-year-old salesman, was admitted on January 23, 1947, complaining of typical ulcer distress of three years' duration. He had vomited frequently, and for the past month the pain had been very severe, especially at night. Two years previously he had an episode of tarry stools. Roentgen ray examination in December, 1946, showed a large ulcer crater in a deformed duodenal bulb without obstruction. Roentgenogram of the gallbladder revealed stones. On January 25, 1947, his night secretion was 2440 cc. with a free acidity of 39 clinical units and a total acid output of 95 milliequivalents. On January 27, 1947, vagotomy and cholecystectomy were performed under spinal anesthesia. The ulcer was found to be on the gastric side of the pylorus. Three weeks after operation the patient had recurrence of ulcer distress accompanied by vomiting. Roentgen ray examination on February 19, 1947, showed persistence of the crater in the pyloric canal, but it was smaller in size. Distress persisted, and on March 11, 1947, roentgen ray examination showed that the crater was still present. On March 27, 1947, the night secretion was 840 cc. with no free acid, and on May 13, 1947, 650 cc. with no free acid. Two insulin tests were negative. On May 16, 1947, a sub-total gastrectomy was performed. Examination revealed the resected ulcer to be located just on the gastric side of the pylorus on the lesser curvature (Fig. 1). Microscopically it was benign. Eight months after operation he was relieved of ulcer distress but could not eat fatty foods and had lost about eight pounds in weight. When last seen in December, 1948, he had no ulcer pain, but complained of moderate diarrhea.

W. H. R., a 32-year-old farmer, first came to the clinic on May 7, 1948. He gave a history of epigastric distress and pain under the lower sternum beginning in November, 1941, and persisting with temporary intermissions to the time of admission. The pain was usually constant, but was relieved by the ingestion of food and alkalies. One episode of severe hematemesis with associated tarry stools occurred in 1941, requiring repeated transfusions. Roentgen ray examination revealed an ulcer in the stomach. There were no further episodes of bleeding, but the epigastric distress persisted in spite of a fairly accurate medical management. Fluoroscopic examination on May 8, 1948, failed to reveal a lesion in the stomach or duodenum. The night secretion averaged 550 cc. with no free acid. A laparotomy was performed on May 10, 1948, and the abdomen was carefully explored without finding any evidence of disease. The stomach and duodenum appeared normal throughout, and there were no scars or adhesions present. The pylorus was patent. The stomach was not opened, but in view of the previous episodes of hemorrhage with symptomatology of peptic ulcer, a vagotomy was performed. Convalescence was complicated by more than the usual amount of gastric stasis, although there was complete relief of the former epigastric distress. Fluoroscopic examination on August 2, 1948, showed marked gastric stasis but there was no evidence of an organic lesion in the stomach or duodenum. The nocturnal gastric secretion on October 31, 1948, averaged 330 cc. in a 12-hour period, with no free acid and 27 clinical units of total acidity. The insulin test was negative. Recurrence of epigastric distress similar to that experienced before the vagotomy was noted in October, 1948, and this rapidly became more severe. Gastroscopic examination on October 30, 1948, revealed an ulcer interpreted as benign on the anterior wall of the mid-portion of the body of the stomach. Fluoroscopic examination on November 2, 1948, revealed a gastric ulcer with a crater, demonstrated by a niche 25 mm. in length, along the midportion of the lesser curvature of the stomach. A second gastroscopic examination on November 1, 1948, again revealed a large benign ulcer on the anterior wall near the lesser curvature in the mid-portion of the stomach. On November 3, 1948, a sub-total gastric resection was performed. The resected specimen revealed a large, typical, benign gastric ulcer on the posterior wall of the stomach near the lesser curvature (Fig. 2). The ulcer crater measured 1.5 cm. in length by 7 mm. in width and 5 mm. deep. The wall surrounding the ulcer was thickened and the mucosa granular. Microscopically there was marked infiltration of the mucosa with round cells, including plasma cells, and

FIG. 1

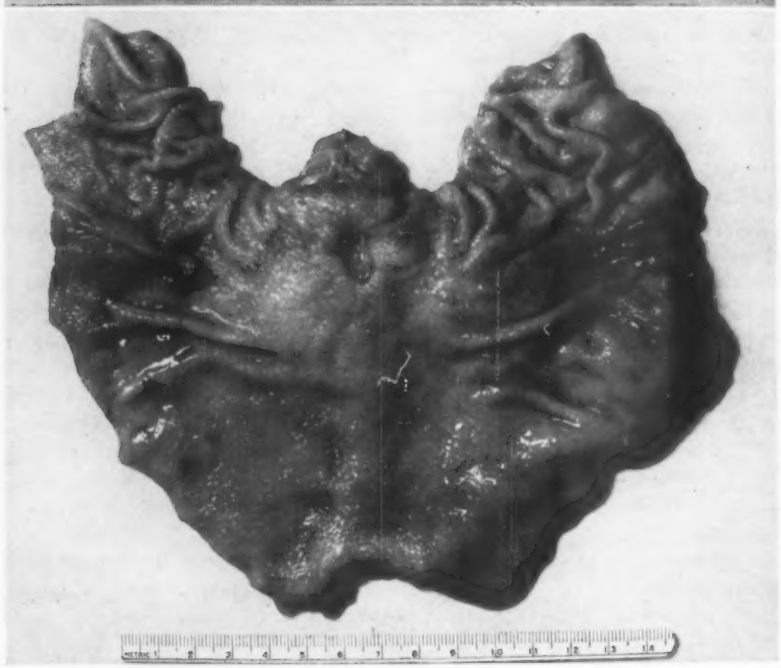

FIG. 2

FIG. 1.—Photograph of resected stomach showing benign pre-pyloric ulcer four months after vagotomy with negative insulin tests afterward.

FIG. 2.—Photograph of resected stomach showing benign gastric ulcer five and one-half months after complete vagotomy.

near the muscularis mucosa there were numerous large reactive lymphoid nodules. The sub-mucosa was fibrotic and invaded by lymphocytes, plasma cells, and eosinophils. The serosa, however, and the mesogastrium, were thickened and hyperemic, and the fatty tissue somewhat fibrotic. The ulcer had penetrated the main muscle coats and undercut the gastric mucosa, particularly on its distal border. Its surface was made up of exudate. Immediately under this region was quite dense granulation tissue with focal fibrinoid degeneration. Recovery from the partial gastrectomy was uneventful, and when last seen on April 4, 1949, the patient was feeling quite well, working every day, and was without epigastric distress or diarrhea. He complained of moderate feelings of fullness and distention after eating.

P. B., a 64-year-old physician, gave a history of intermittent gastric pain and distress for 14 years, with roentgenogram demonstrating a duodenal ulcer on several occasions. There had been one episode of hematemesis in 1933; and he had had recent night pain. The patient brought outside roentgenograms which demonstrated a healed duodenal ulcer and a new ulcer crater on the lesser curvature of the stomach; according to the history this crater had originally been seen in 1939. There was no history of obstruction or co-existent disease. Medical management had been good. Laparotomy on November 24, 1947, showed a scar and an adhesion of the old ulcer in the first portion of the duodenum. There was no evidence of obstruction. On the lesser curvature of the stomach on the mid-section was an indurated area with a perforating ulcer whose crater could be felt. A subdiaphragmatic vagotomy was performed. Postoperatively there was a temperature elevation of 38 to 39 degrees rectally for two days which may have been due to a mild atelectasis. A six-week follow-up showed moderate diarrhea, decreasing in severity since the time of operation. There was no ulcer distress but there were mild symptoms of stasis. The patient's weight gain progressed to 26 pounds in November, 1948, when, for the first time, ulcer distress recurred. An insulin test was negative seven months postoperatively but was positive on December 14, 1948; nocturnal secretion was of low volume with no free acidity. Roentgen ray revealed a lesser curvature gastric ulcer and a sub-total gastrectomy was performed on December 15, 1948. A benign ulcer, recurrent at a previously involved site, was found on pathologic examination of the specimen. In January, 1949, the patient was making a favorable convalescence without ulcer distress.

H. A., a 46-year-old machinist, was admitted to the clinic complaining of typical ulcer distress for the previous eight years. He had had no night pain, no hemorrhages, no perforation, and no obstructive symptoms. Medical management had been excellent and had included a course of roentgen ray therapy to the fundus of the stomach. Repeated roentgen ray examinations since 1942 had demonstrated a recurring, benign, gastric ulcer with hour-glass deformity of the stomach. On November 22, 1946, the night secretion was 861 cc., with no free acid, and the insulin test was positive. On December 4, 1946, a transabdominal vagotomy was performed under spinal anesthesia. A firm, freely movable mass could be felt high on the lesser curvature of the stomach. On December 12, 1946, one insulin test was negative. Gastroscopy on July 2, 1947, showed considerable gastric retention and a possible superficial ulcer. In October, 1947, he complained of recurrent epigastric distress which was considered to be ulcer distress. Roentgen ray examination on November 5, 1947, revealed an hour-glass contraction but no definite crater. Eighteen months postoperatively he continued to have pains similar to his preoperative distress. Roentgenogram on June 23, 1948, revealed persistent deformity of the greater curvature of the stomach with no evidence of a crater.

The development of benign gastric ulcer in patients who have previously had a vagotomy for duodenal ulcer with subsequent healing presents an interesting phenomenon. We have had one proved case of this type and there is possibly a second as yet unconfirmed.

The first patient to have a complete vagotomy in this clinic, W. B., a white male, age 51 years, had been operated upon in 1930 for a perforated peptic ulcer. He felt well until 1938, when he developed epigastric pain which was most severe two hours after the noon meal and at 2:00 A.M. This pain was relieved by food, alkalies, rest, or vomiting. Fluoroscopic examination on December 8, 1942, revealed high-grade pyloric stenosis with a large ulcer crater. Nocturnal gastric secretion averaged 1160 cc. with a free acidity of 65 clinical units, and a total hydrochloric acid output of 75.4 milliequivalents. On January 18, 1943, a transthoracic vagotomy with resection of 3 cm. of both vagus nerves was performed. The ulcer distress promptly disappeared and the nocturnal gastric secretion was reduced to 310 cc. with a free acidity of 58 clinical units and a hydrochloric acid output of 18 milliequivalents. There was evidence of marked stasis of food in the stomach, but the patient continued free from distress and in good general condition for about four years. In 1947, typical ulcer distress recurred and gastroscopy revealed a large ulcer on the posterior wall of the stomach near the lesser curvature. The insulin test was repeatedly

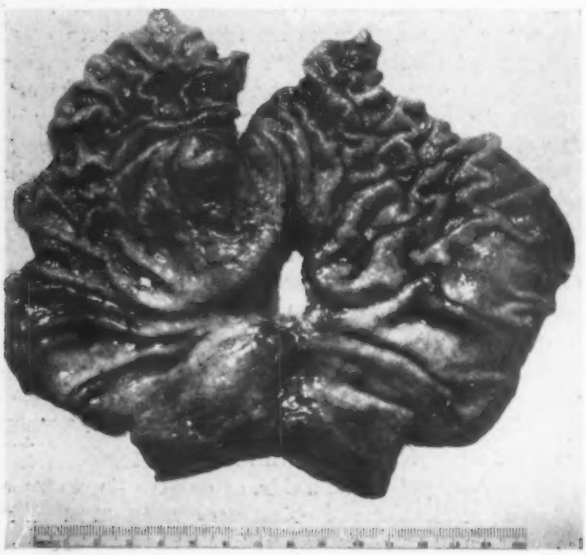

FIG. 3.—Photograph of resected stomach showing gastric ulcer penetrating into the pancreas which developed four years after complete vagotomy for duodenal ulcer. Duodenal ulcer remained healed.

negative and the nocturnal gastric secretion averaged 620 cc. with no free acid. A carcinoma was suspected and a sub-total gastrectomy was performed April 11, 1947. The resected specimen disclosed a large benign gastric ulcer (Fig. 3) with marked intimal proliferation and thrombosis in the blood vessels in the neighboring gastric wall (Figs. 4 and 5).

Of a total of nine patients in our series with both gastric and duodenal ulcers five had vagotomy alone and four vagotomy plus gastroenterostomy. One patient has been lost to follow-up and six are free of symptoms at the present time. One died of intra-cranial hemorrhage six weeks after the vagotomy and at autopsy the duodenal ulcer was healed, the gastric ulcer partially healed. One patient died in the immediate postoperative period of

FIG. 4

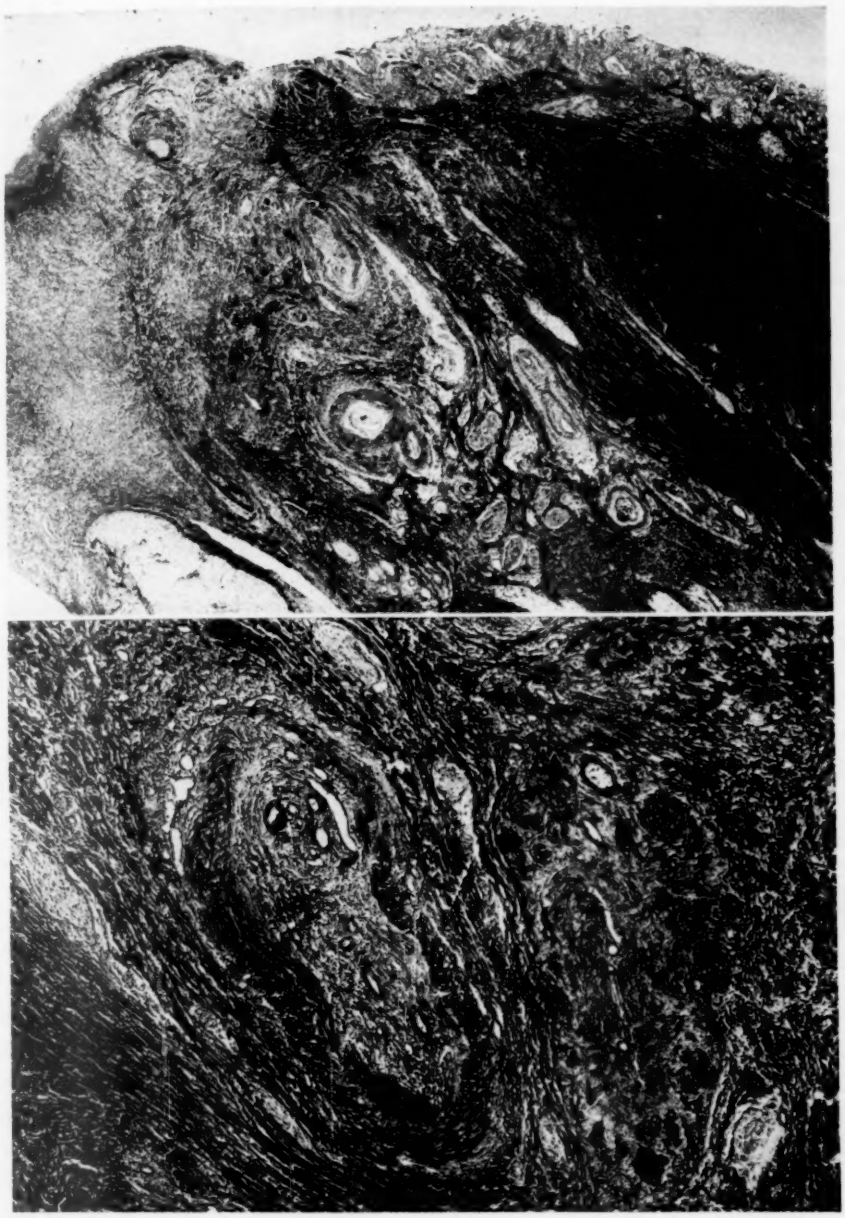

FIG. 5

FIG. 4.—Photomicrograph showing intimal proliferation, thrombosis, and re-canalization in vessels in gastric wall near the ulcer seen in Figure 3.

FIG. 5.—Higher magnification showing details of thrombosis, organization, and re-canalization of vessels in Figure 4.

persistent bleeding from the gastric ulcer. This history is summarized as follows:

R. W., a 65-year-old white male, was admitted to the clinic on July 11, 1947, complaining of typical ulcer distress for the previous 30 years. Medical management had been inadequate. He was in profound alkalosis as a result of persistent vomiting when he came to the hospital. Fluoroscopic examination revealed high-grade pyloric obstruction with marked gastric retention. On July 20, 1947, following hematemesis and melena, the patient went into vascular collapse necessitating repeated transfusions. On July 22, 1947, he was transferred to surgery, where supportive therapy was continued, and the patient received 3 more transfusions. Although still in a precarious state and with moderate alkalosis, on July 24, 1947, a laparotomy was performed. Exploration of the stomach revealed a crater on the lesser curvature, 3 cm. from the esophagus, and a duodenal ulcer with obstruction. A vagotomy and posterior gastroenterostomy were performed. The postoperative course was stormy with persistent high fever, and the blood pressure frequently fell to shock levels, and the patient required oxygen. On July 29, 1947, he had a massive internal hemorrhage, and five blood transfusions were given. The blood pressure stabilized on the following day, but then he had another massive hemorrhage, and accordingly, on July 30, 1947, he was re-explored. The stomach was opened and found to be filled with a large blood clot which, when removed, revealed a large shallow ulcer crater on the lesser curvature. In the center of the ulcer an arteriosclerotic artery was seen spurting blood. This was ligated with a mattress suture and the abdomen closed. The patient's condition failed to improve in spite of repeated transfusions and other supportive measures. Aspiration pneumonia developed, and death occurred on August 13, 1947.

TABLE I.—*Average Twelve-Hour Night Gastric Secretion in the Empty Stomach of Normal Individuals and Peptic Ulcer Patients.*

	Number of Cases	Volume in CC.	Free Acid in Clinical Units	HCl Output in Milliequivalents
Normals	33	581	31	18
Normals (prison)	23	621	44	30
Duodenal ulcers before vagotomy	135	1,085	52	60
Duodenal ulcers after vagotomy	70	521	22	11
Gastric and duodenal ulcers before vagotomy	8	1,106	38	42
Gastric and duodenal ulcers after vagotomy	8	459	12	5.5
Gastric ulcers before vagotomy	14	773	23	17.8
Gastric ulcers after vagotomy	10	465	3	1.4

In our previous report[1] we commented on the fact that hypersecretion of gastric juice was not found in patients with gastric ulcer, although this was the usual finding in duodenal ulcer. Subsequent experience has confirmed this observation, and is well illustrated in Table I, which displays the volume, free acidity, and total acid output in the nocturnal secretion of patients with various types of peptic ulcer compared with normal individuals. It is probable that the most significant figures are those in the fifth column, recording the total output of hydrochloric acid in the empty stomach in a 12-hour period. This figure is obtained by multiplying the volume of secretion in liters by the concentration of hydrochloric acid in clinical units. The product represents the 12-hour output of hydrochloric acid in milliequivalents. The volume and free acid concentration are of lesser meaning, since there is usually

contamination of the parietal secretion by saliva or regurgitated duodenal content.

Thirty-three normal individuals secreted an average of 18 milliequivalents of hydrochloric acid, and 14 gastric ulcer patients 17.8, or almost an identical amount. In contrast to this, 135 patients with duodenal ulcers secreted 60 milliequivalents, or three times the normal value. Eight patients with both gastric and duodenal ulcers secreted 42 milliequivalents of hydrochloric acid. In the duodenal ulcer patients the nocturnal acid secretion was reduced to 11 milliequivalents by vagotomy, or less than the normal level, and in the gastric ulcers the secretion of acid was almost abolished. In the patients with both gastric and duodenal ulcers there was also a marked reduction in acid secretion to 5.5 milliequivalents.

Several recent authors[2, 3] have called attention to striking differences in gastric and duodenal ulcers with respect to total incidence, sex incidence, response to therapy, and other factors. Surgeons have been impressed with the fact that whereas gastrojejunal ulcers frequently were seen following gastroenterostomy or small gastric resections for duodenal ulcer, they were almost never seen when similar operations were done for gastric ulcer. Differences have now been demonstrated in gastric secretion and in the response of these lesions to complete vagotomy. Can these observations be harmonized with the experimental studies on the pathogenesis of ulcer?

The capacity of pure gastric juice to erode the normal mucosa of the stomach and intestines and thus produce a progressive peptic ulcer has been amply demonstrated by controlled experiments in laboratory animals.[4] Ulcers do not appear under normal conditions because the gastric content is made up of not only gastric juice but substances such as food, saliva, pyloric mucus, and duodenal secretions which dilute and buffer the pepsin-hydrochloric acid. These neutralizing factors constitute a local protective mechanism against ulcer formation which is usually adequate. Removal of the duodenal secretions from the upper intestinal tract reduces the efficiency of this protective mechanism, and when this is done in experimental animals as in the method of Mann and Williamson,[5] ulcers regularly are produced. A defect of this type has been demonstrated to occur only rarely in man[6] and probably plays a small role in the clinical problem of ulcer disease. A decreased production of gastric mucus, which comes chiefly from the antrum, has been sought for in ulcer patients, and while some suggestive findings have been reported, no definite conclusions can be made. On the other hand, an increase in the corrosive properties of the gastric content due to hypersecretion of gastric juice in response to the physiologic stimulus of food, and more importantly in the empty stomach as well, has been demonstrated in the great majority of duodenal ulcer patients. An excessive nocturnal secretion in these cases has been almost invariably present in our experience.[7, 8] Both the hypersecretion of the empty stomach and the exaggerated response to food intake have been abolished by complete removal of the vagus innervation of the stomach,

indicating that they are of neurogenic origin. Usually, relief of ulcer distress and objective evidence of healing have paralleled the decrease in acid in the gastric content, and both may be ascribed to this effect.

In gastric ulcer, however, a hypersecretion of gastric juice has not been found, and as a consequence the corrosive properties of the gastric content due to the concentration of hydrochloric acid and pepsin are not greater than in normal individuals. This would suggest that these ulcers are due to a local loss of resistance to gastric digestion, which may in some cases be vascular thrombosis, as called for in the theory of Virchow and Hanser and exemplified in case W. B. in this report.

We cannot conclude that digestion of the gastric wall by pepsin-hydrochloric acid plays no role in the genesis of gastric ulcers, since as W. L. Palmer[9] has repeatedly pointed out, acid is always present in these cases if carefully looked for, and medical management with antacid therapy cures many of them. Also it should be pointed out that most of the gastric ulcers in our series healed following vagotomy, and that this healing was usually accompanied by a marked reduction or abolition of free acid in the night secretion.

The concept of a primary difference in pathogenesis between gastric and duodenal ulcers may be useful in directing therapy. Hypersecretion with resultant increase in the corrosive properties of the gastric content in duodenal ulcers calls for measures to reduce the hypersecretion. Since this hypersecretion is neurogenic in origin, vagotomy appears to be the logical procedure. Vagotomy is clearly less indicated in gastric ulcers, since hypersecretion is not present, and in any case the possibility of cancer dictates a partial gastrectomy whenever practicable.

Gastrojejunal ulcer clearly belongs with duodenal ulcer in pathogenesis. Here a previously normal area of jejunal mucosa succumbs when exposed to the digestant action of the gastric content. It is not digested away by the normal content, as is evidenced by the absence of stoma ulcers when gastroenterostomy is done for gastric ulcers or pyloric cancers, or when performed in normal dogs. Stoma ulcers are commonly found following gastroenterostomy in duodenal ulcer patients with excessive nocturnal secretion. The fact that antrum resection does not prevent gastrojejunal ulcers is further evidence that nervous factors are more important in these lesions, and this conclusion is borne out by the favorable response of these ulcers to vagotomy.

A deleterious effect of gastric stasis is indicated in this study. The patient who developed a gastric ulcer four years after vagotomy for duodenal ulcer had persistent severe retention. Although he had a stenosing duodenal ulcer, a supplementary gastroenterostomy was not performed because the vagotomy was done by the transthoracic approach and at that stage in our study it was considered essential to determine the effect of the vagotomy alone. Two of the patients with gastric ulcers that failed to heal following vagotomy had persistent gastric stasis. A supplementary gastroenterostomy was not usually

done in patients with gastric ulcers because this was thought to be unwise in the absence of organic obstruction.

While the major cause of gastric stasis following vagotomy is undoubtedly the marked reduction in the tonus and motility of the body of the stomach following the procedure, an important factor in many cases is pylorospasm of varying degree. This is indicated by the fact that when gastroenterostomy was performed in addition to vagotomy in 262 patients in our series, retention in the immediate postoperative period was less and resumption of normal emptying occurred sooner than in those with vagotomy alone. Since we are now persuaded that vagotomy protects against the development of gastrojejunal ulcer, posterior gastroenterostomy has been adopted as a routine procedure when vagotomy is performed for duodenal ulcer. It is quite possible that had gastroenterostomy been done in addition to vagotomy in the gastric ulcers in this series, the results might have been better.

In a recent report[10] Finsterer gives an account of 614 operations he has performed on ulcers in the region of the cardia. In 79 of these, the ulcer was left in situ and the lower half of the stomach removed after the method of Kelling and Madlener. The operative mortality was 5 per cent, and about 90 per cent of the patients remained free of pain. The beneficial effect of this operation probably depends on the reduction in gastric secretion secured through removal of the antrum. In a series of experimental studies, my associates E. R. Woodward and R. R. Bigelow, and I have recently determined that of the total gastric juice produced in dogs, roughly 40 per cent is secreted in response to vagal stimuli, 40 per cent from the stimulation from the antrum, and 20 per cent from the intestines. It is accordingly probable that vagotomy produces just as great a reduction in gastric secretion in gastric ulcer patients as would be secured by the Kelling-Madlener operation, and if combined with a gastroenterostomy to control the factor of pylorospasm, would accomplish just as much by a more conservative operation.

CONCLUSIONS

1. In a group of 17 patients with gastric ulcers treated by vagotomy alone, the ulcer failed to heal or recurred in five or 29 per cent. In three of these the vagotomy was complete.

2. In a group of 197 patients with duodenal ulcers treated by vagotomy alone, gastric ulcers subsequently developed in two, although the vagotomy was complete and the nocturnal hypersecretion abolished in both instances.

3. In a group of 262 patients with duodenal ulcers treated by vagotomy and gastroenterostomy, no gastric ulcers have so far appeared.

4. In patients with duodenal ulcers, and in those with co-existing duodenal and gastric ulcers, the output of hydrochloric acid in the nocturnal fasting secretion is from three to four times the amount in normal individuals.

5. In patients with gastric ulcers the output of hydrochloric acid in the nocturnal fasting secretion is the same or less than that in normal people.

6. Complete vagotomy produces a much greater decrease in the output of hydrochloric acid in duodenal than in gastric ulcers (a ratio of 49 to 16.4 milliequivalents).

7. The absence of gastrojejunal ulcers following partial gastrectomy or gastroenterostomy for gastric ulcer or pyloric cancer in man or following gastroenterostomy in dogs indicates that the jejunal mucosa can resist the digestant action of the gastric content when the secretion of gastric juice is within the normal range, or depressed.

8. The frequent occurrence of stoma ulcers following gastroenterostomy or antrum resection for duodenal ulcers indicates that the jejunal mucosa cannot resist the digestant action of the gastric content when hypersecretion exists, and furthermore, that this hypersecretion is not abolished by removal of the antrum.

9. The healing of duodenal ulcers following vagotomy and the absence of gastrojejunal ulcers following combined vagotomy and gastroenterostomy, indicates that both of these ulcers are due to the increased corrosive properties of the gastric content as a result of hypersecretion.

10. The absence of hypersecretion in gastric ulcers suggests that these lesions are not due to an increase in the corrosive properties of the gastric content but rather to a decrease in resistance on the part of the gastric wall.

11. Vagotomy is not indicated in the treatment of gastric ulcers because hypersecretion of neurogenic origin is not present, and because sub-total gastrectomy may accomplish something in the way of therapy should the lesion prove to be cancerous.

12. For juxta-esophageal ulcers vagotomy and gastroenterostomy will probably accomplish as much as the Kelling-Madlener operation. Total gastrectomy is not warranted in these cases in the absence of proved cancer. Sub-total gastrectomy does not remove these lesions with a sufficient margin to have therapeutic significance should the disease prove cancerous.

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Editorial . .

The Place of Research in a Surgical Training Program

It is self evident that all surgeons will not be productive investigators. Even among those selected for residencies in teaching hospitals, there are many who will not be of much value to society in this way. The questions arise, therefore, why place so much emphasis on research in the training of young surgeons? Would it not be better to segregate those with an interest and aptitude for research from the others? Would it not be better to detach those who are interested from clinical training for periods of investigation, so that their research activities will not interfere with the smooth functioning of a clinical service?

There is, of course, no one set of answers to these questions. The value of an outstanding contribution to surgical science is so great as to be hard to overestimate. Therefore, those institutions so situated as to be in the forefront of scientific advance are certainly justified in planning their overall programs so as to enhance the probability of successful research as far as possible. They often need their residents to provide the medical man power required.

Another consideration stems from the fact that much which is published as new and worthwhile is little more than conjecture and opinion. It is obviously important that clinicians who are not investigators themselves, nevertheless develop judgment and skill in evaluating the work of others. Probably nothing gives quite so much insight in this regard as the experience of collaborating in a research project at first hand.

Thus, in teaching hospitals with research facilities, we have two good reasons for expecting men taking surgical training to participate in research activities; first, to provide the man hours to carry forward such work and, second, to give the trainee experience which will strengthen his critical judgment of investigative work.

There are other possible reasons for exposing such a comparatively large group of men to this type of experience. Occasionally an able man without much interest in original work will catch the fire of an older investigator and develop an interest of his own. This is rare in our experience, but it is common for those who have an interest to find it strengthened through use or for it to fade out through disuse. More important is the mind set which one gets toward his clinical work in an institution where everyone is trying to add to the sum total of surgical knowledge, that is, to do more for patients than established methods have accomplished in the past. This is essential in the training of the best clinicians, yet it is derived for the most part from a spirit of investigation.

In those institutions in which almost all surgical trainees are expected to share in the responsibility for the advance of knowledge, the question arises as to how this is best accomplished. Should a man be allowed to concentrate entirely on his clinical work for a stretch of time and then be provided with leisure for full time research, or should he be expected to carry both concurrently? Heavy as the pressure of clinical work may be on the trainee, it is not likely to be less demanding when his training is finished and he is well established as a clinician in his own right. Therefore, it seems to this author that unless a man learns to carry a load of investigative work concurrently with clinical work during his residency, it is not likely that he will get any research done after his training is completed unless he becomes a full time investigator.

On the other hand, if both activities are to be engaged in concurrently, it is essential that the clinical load be shared widely enough so that it does not require all the time and energy of the individual. When the clinical load is permitted to approach this latter level, the ability to make progress with a research problem becomes a function of stamina and work tolerance rather than a function of originality and perspicacity.

The whole question of the place of the clinician in research is one that demands careful consideration. While a period of clinical work may be helpful in the orientation of a full-time laboratory investigator, the major advantage of combining research and clinical training seems to consist in having men with knowledge of and capacity in research methods in day to day contact with the problems of the patient. It should be their special opportunity to recognize significant problems and to pick out those which may be susceptible of solution by the technics made available by full time laboratory investigators.

To the extent that this generalization is true, it would seem that in surgery we should aim, not exclusively, but for the most part, to train investigators who will remain in clinical work. While periods of full-time research often have a place as part of the training program, periods of full time clinical work, from which research is excluded, are not conducive to the training of men who are to continue in investigative work after they become clinicians in their own right. It is of the greatest importance that they form a strong habit of devoting time to the search for new knowledge at the same time that they perform their clinical duties carefully and conscientiously.

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